INTRACELLULAR AND IMMUNE-RESPONSE DELAYS EFFECTS ON THE INTERATION BETWEEN TUMOR CELLS, ONCOLYTIC VIRUSES AND THE IMMUNE SYSTEM

by

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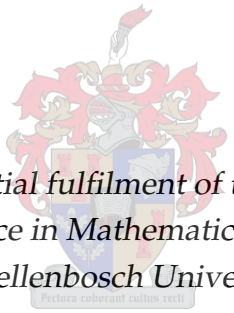

Thesis presented in partial fulfilment of the requirements for the degree of Master of Science in Mathematics in the Faculty of Science at Stellenbosch University

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Abstract

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ABSTRACT

Lately, oncolytic viruses have been used to mitigate cancer as they lyse tumor cells whilst leaving normal cells largely unharmed (as opposed to many other forms of cancer treatment). The oncolytic effect depends on both viral replication ability and immune response type induced by said replication. A major challenge posed by this therapy is any potential delay that can occur during viral replication, combined with a fast immune response. For this project, we will investigate possible trade-offs of the interactions, with particular focus on the effect(s) of delay.We will extend recently published mathematical models on virotherapy by taking into account the simultaneous effect of the delay and considering various forms of virus-cell infections. We perform stability analysis with the delay and run numerical simulations to confirm the mathematical findings and see

how well this model would fit data or whether by the introduction of the delay terms, we improve the fit of the data. Eventually, we derive an explicit formula for the trade-off between the two delays that leads to tumor eradication. One of the main findings is the occurrence of a delay-induced Hopf bifurcation, indicative of tumor relapse which is a confirmation of other previous cancer virotherapy mathematical models.

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Onkolitiese virusse word die afgelope tyd gebruik om kanker te versag, aangesien hulle tumorselle lig, terwyl normale selle grootliks ongedeerd bly (in teenstelling met baie ander vorme van kankerbehandeling). Die onkolitiese effek is afhanklik van sowel die virale replikasievermoë as die immuun-re-sponse tipe wat deur genoemde replikasie veroorsaak word. 'n Groot uitdaging wat hierdie terapie inhou, is die potensiële vertraging wat tydens virusreplikasie kan voorkom, gekombineer met 'n vinnige immuunreaksie. Vir hierdie projek ondersoek ons moontlike inruilings van die interaksies, veral met die oog op die gevolge van vertraging. Ons brei wiskundige modelle oor viroterapie wat onlangs gepubliseer is, uit deur die gelyktydige effek van die vertraging en die oorweging van verskillende vorme van virusselinfeksies in ag te neem. Ons doen stabiliteitsanalise met die vertraging en voer numeriese simulasies uit om die wiskundige bevindings te bevestig en te bepaal hoe goed hierdie model by die data sou pas, of deur die inwerkingtreding van die vertragingsterme die pas van die data te verbeter. Uiteindelik verkry ons 'n eksplisiete formule vir die verhandeling tussen die twee vertragings wat lei tot die uitwissing van gewasse. Een van die belangrikste bevindings is die voorkoms van 'n vertraging-geïnduseerde Hopf-bifurkasie, wat 'n aanduiding is van tumor-terugval, wat die bevestiging is van ander vorige wiskundige modelle vir kankerviroterapie.

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Dedications

In loving memory of Marie Wanja Njeru; a friend, a cousin, a 6 year old relentless stage 4 cancer victim.

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Chapter 1

Introduction

1.1 Introduction

Cancerous ailments have become a major cause of death world over in recent years. (Sudhakar, 2009).

According to statistics by bodies such as GLOBOCAN (International agency for research on Cancer, 2018), last year, almost 2 million new victims came from the USA. Almost half of these cases projected to result in death (Siegel *et al.*, 2017). We can therefore deduce that this epidemic requires keen interest has to be taken to alleviate this problem (Danaei *et al.*, 2005).

There has been advancement in research and medicine to mitigate its effects and minimise the cases of cancer victims since its discovery in ancient Egypt around 1500 BC when only palliative treatment was offered. In (Sajid *et al.*, 2008; Saunders, 1991),the authors describe this as just general taking care of a seriously ill patient who cannot be cured.

Cancer has still persisted especially in recent years and has been attributed to lifestyle habits such as smocking of tobacco which has been said to cause lung cancer (Sajid *et al.*, 2008). Other cancers can be caused by chemical carcinogens, radiation or viruses. Cancer may also be hereditary.

Moreover, genes play a huge role in how cancer occurs. There are two main types of genes: **a) Oncogenes**, which facilitate abnormal growth of otherwise normal cells to

form tumors through mutations of prorooncogenes which control the frequency of cell division and differentiation degree and **b) Tumor suppressor genes** which control cell division and cell death. Once these genes malfunction, they cause an abnormal growth in normal cells causing cancer (Sudhakar, 2009).

There are a couple of methods for treating cancer, these include Chemotherapy, Radiotherapy, Hormonal therapy, Immunotherapy, Stem-cell transplants and Adjuvant therapy (Sudhakar, 2009). These therapies do not seem to fully work and one of their biggest pitfalls is harming normal cells during treatment (PosthumaDeBoer *et al.*, 2011). If cancer is detected in its early stages, it may be curable. However, in other cases where the tumors can be removed or significantly reduced, the tumor(s) may later relapse depending on their classification and location (Rutqvist *et al.*, 1984).

Researchers and doctors have sought a novel treatment called **oncolytic virotherapy** (Kirn *et al.*, 2001).It involves treatment via virus able to replicate and clear tumor cells leaving normal ones healthy (Russell *et al.*, 2012).

Exact timing of when oncolytic viruses were discovered is vague, however, in 1886, it was "accidentally" noted that a woman suffering from *leukemia* was temporarily relieved after contracting flu (Dock, 1904), . Her previously distended liver and spleen deflated to their conventional proportions and the number of her white blood cells improved significantly too. Around the same period, A male toddler suffering from *lymphatic leukemia* was taken ill by varicella, which is a viral disease characteristic of a rash. As was the case of the woman too, his leukocyte count also improved greatly. The century that followed saw modern medicine facilitate improvement on this mode of treatment, with Chinese regulators approving the first marketing of an oncolytic virus (adenovirus H101) in November 2005 (Kelly and Russell, 2007).

Oncolytic virotherapy is an alternative mode of treatment which has triggered a lot of clinical research (Kirn, 2001; Kirn *et al.*, 2001; Lawler *et al.*, 2017; Liu *et al.*, 2007; Pol *et al.*, 2016). Mathematical modelling was also used to help understand this novel mode of treatment (Bajzer *et al.*, 2008; Crivelli *et al.*, 2012; Dingli *et al.*, 2006; Paiva *et al.*, 2009). Most models have considered the rate of infection as well as clearance (of the virus), measure of cell death and burst size (amount of new viruses produced once a tumor cell gets infected (Bajzer *et al.*, 2008; Malinzi *et al.*, 2017; Tian, 2011)) as the only key factors of oncolytic viruses. In addition to the above, it is imperative to further take into account a) how fast/slow the virus would replicate and b) how strong and/or fast the anti-viral

immune response would be.

It is with this regard that some mathematical models have considered taking delays into account. We have the intracellular delay, herein described as time taken from when the virus binds to the tumor cell to the proliferation of more cells (Tian *et al.*, 2016; Xu, 2011)

The other is the immune response delay which is modelled as time taken by the immune system to invoke a suitable response once it recognises the virus-infected cells (Crivelli *et al.*, 2012; Prestwich *et al.*, 2008; Timalsina *et al.*, 2017; Wang *et al.*, 2013)

Although delays have been individually modelled, as at this time, it's the first attempt at analysing the out-turn of both delays in tandem.

In this thesis, we table a mathematical model having a duet waiting period with our aim being to find a trade-off between the two delays that would lead to tumor elimination or control.

1.1.1 Thesis outline

We present this work in six chapters. For the opening chapter, we give an overview of the history of cancer, current statistics and treatment methods and give insight on oncolytic virotherapy. In chapter two, we delve into the literature review where we unpack the different types of cancer and how they spread and expound on oncolytic virotherapy. The third chapter contains some mathematical preliminaries on delay differential equations needed for the analysis of the model with delays. We have an overview of simple mathematical models which do not consider delays in the following chapter and carry out their equilibria and stability. We also look at a previously simple analysed model. For chapter five, we introduce delays, carry out some analysis for their equilibria as well as use the DDE23 solver to perfom simulations and present the results in the same chapter. To wrap up the thesis, we discuss the findings as well as shortfalls of the models we chose and make a reference to work we intend to embark on in future to further the study.

Chapter 2

Literature Review

2.1 Introduction

In this chapter, we present a literature review of the burden of cancer; epidemiology of cancer, its risk factors and treatment. A special focus will be given to oncolytic virotherapy which consists of using viruses that are able to infect and destroy cancer cells while keeping normal cells unharmed.

2.2 Literature review

Cancer is a huge life-threatening epidemic. Over the past two decades, mortality rates from all cancers fell by 17% in those aged between 30 and 60 years while for septuagenarians and older, the mortality rate rose by 0.4% (Danaei *et al.*, 2005)

It is a name given to a group of similar diseases which come about by the non-stop division and spread of some of the body cells and eventual spread into surrounding tissues (National Cancer Institute, 2015).

Cancer can be grouped into five main categories each with characteristics unique to their individual group. These include: **Carcinomas** - listed as the most prevalent type of cancer such as prostate, breast, lung and colorectal cancers, they occur on the skin and/or tissues lining internal organs and glands forming solid tumors; **Sarcomas** - these develop in connective tissues such as: bones, cartilage, fat, muscles, nerves, tendons, blood vessels and lymph vessels; **Leukemia** - these are a group of cancer cells in the blood and/or bone marrow. It includes several types of leukaemia. **Lymphomas** are

cancer cells that attack a body's immune system starting from the lymphatic system which mitigates infection. It is characterized by two types, namely, Hodgkin and non-Hodgkin lymphomas; and lastly, **Central nervous system cancers** developing within the brain and the spinal cord. (American Society of Clinical Oncology, 2018; Cancer Centre, 2018)

While patients can suffer from a similar type of cancer such as leukaemia, cancer cells may vary from one individual to another due to variations in their cell structure and chemistry. Recent research has seen classification of cancer groups into sub-groups. (Cancer Centre, 2018)

In a healthy individual, cells divide to form new ones. They later die when they become old and damaged and consequently are replaced by new cells. In the unfortunate case that this systematic order is disrupted or breaks down, the cells become abnormal and survive instead of dying and new ones form where they aren't required. This continuous division may then form malignant growths called *tumors.* (National Cancer Institute, 2015)
Growth of tumors is attributed to the fact that cancer cells aren't as specialized as normal cells and therefore not maturing into different cell types with individual functions, which causes them to multiply at a faster than that of the neighbouring cells. Many solid tumors are masses of tissues except in the case of blood cancer, known as *leukemia,* which isn't characterised by solid tumors. (National Cancer Institute, 2015)

However, extensive research over the last century suggests that solid tumors do not necessarily lead to death, but metastasis of the tumors do. Actually contributing 90% of deaths in these types of cancers (Gupta and Massagué, 2006). Metastasis herein, refers to a two-step process where firstly, the unstable cells attach themselves to a tissue far from the initial growth (Gupta and Massagué, 2006), and later, these cells develop into a new growth (Chaffer and Weinberg, 2011).

Cancerous tumors are dangerous since as they grow, they also destroy nearby cells. They can also get transported all around the body, leading to the creation of new tumors where they arrive (Alfano *et al.*, 1993; Farnsworth *et al.*, 2018). This spreading - metastasis, earlier defined, is the main reason that the detection of cancer prior to spreading is of high importance to minimise severity. Cancer cells are known as malignant while the non-cancerous are known as benign. (Alfano *et al.*, 1993)

There are many types of cancers.(National Cancer Institute, 2015). Of these, only $5-10\%$ are attributed to genetic defects. Environment and lifestyle choices including smoking, poor diet, alcohol, radiation, pollution and infectious organisms among others, cause the remaining $90-95\%$ cases. (Anand *et al.*, 2008)

Depending on extent at first diagnosis, it's grouped into stages ranging from $0-4$. These stages help determine spread and best treatment method(s). Stage 0 is before the cancer spreads. The cancerous cells have not migrated from the area they formed in. In stage 1, the cancer has not spread tolymph nodes and other organs of the body, rather just a little in neighbouring tissues only. Stage $2-3$ means that neighbouring tissues and lymph nodes have been affected while the final stage 4, commonly referred to as metastatic/ advanced cancer means that the cancer has moved to other body parts. Leukaemia is not staged as it spreads throughout the body. (American Cancer Society, 2018; Cancer Institute NSW, 2015)

There are various ways to stage cancer all depending on where it is located. A doctor may either carry out a physical examination or run imaging tests like scans. For results confirmation, a biopsy, which is a medical procedure involving examining of tissue under a microscope in this case to determine presence of cancer cells, is carried out. Most staging is carried out via the TNM(Tumor, Node, Metastasis) system (Cancer Institute NSW, 2015)

On a wider global scale, it is reported that about 6 years ago, there were about 14 million cases reported and over 8 million deaths due to this disease. 57% of the cases occurred in less developed regions such as Africa as well as 65% of death reports. Statistics indicate that new reports each year will spring up to almost 24 million within the next decade. (National Cancer Institute, 2015)

Further note that these regions are the home to over 80% of the world's population. This is mainly attributed to bad lifestyle choices which increase the risk of cancer like cigarette smoking, lack of a proper diet or even changes in reproduction. (Torre *et al.*, 2015)

There are several different modes of treatment which can be offered to a cancer patient depending on the type of cancer they are suffering from, its location and how advanced it is.

Cancer was regarded as an incurable disease until the 19^{th} century when surgical removal was made more efficient and available by use of anaesthesia and improved techniques. Before 1950, surgery was the preferred means of treatment but after 1960, radiation started being implemented as well. Over time however, neither surgery nor radiation or a combination of the two as a means of treatment was adequate to control the metastatic cases of cancer. For better treatment and improved survival rate to be achieved, it was then noted that therapy needed to reach all body parts since sometimes, tumors have been reported as migrating to other parts of the body. That is why current efforts to cure this epidemic are centred around use of drugs, biological molecules and immune mediated therapies (Wu *et al.*, 2006) .

Current cancer-mitigation methods are listed in the following paragraphs.

Chemotherapy, also called *chemo*, is when, drugs are administered to a patient. Research on this form of therapy was started by Ehrlich around 1891 (Hawking, 1963).

This form of treatment either stops or slows down the growth of cancer cells which consequently ensures that the tumor also either dies off completely, stops increasing in size or slows down in terms of growth. It also helps to shrink the tumors that may otherwise cause pain (National Cancer Institute, 2015).

Both the medical practitioner and patient need to carefully consider both the potential risks and benefits of chemotherapy treatment as there is a list of substantial reactions of this treatment. Conventionally, short-term side effects may include neuro and renal toxicity; while long-term side effects may include complications at a later stage such as pulmonary defects arising after the conclusion of appurtenant chemotherapy (Morgan and Rubin, 1998). The drugs agents used in *chemo*, enhance the body's immune response to an antigen after initial treatment. Adjuvant chemotherapy is especially used to suppress secondary tumour formation. Side effects will depend on the type of drugs used, its dosage and treatment period of patient. (Partridge *et al.*, 2001).

Radiotherapy, uses high doses of radiation to enable tumor shrinkage and death of tumor cells. Treatment may be administered either internally or externally. Internal radiotherapy treatment, known as *brachytherapy*, involves having a radioactive implant inserted in the body, in or near the tumor. (**?**). It also helps to treat other problems associated with the tumors for example trouble with breathing. One of the greatest disadvantages is that long and/or frequent exposure to radio waves may lead to the damage

of otherwise healthy tissues (Anscher *et al.*, 2003).

In surgery, the surgeons physically cut off the solid tumors. However, this method of treatment cannot be used to treat leukemia patients as there is no solid mass to extract or patients whose cancers have spread as it could be too risky for the patient and lower the chances of survival. It also carries a high risk of pain and infection which could lead to other complications (Lederman, 1981).

Immune-based treatment involves a biological form of treatment where the immune system is helped to fight the cancerous cells on its own. It consists of either adoptive cell transfer, cytokines, treatment vaccines, BCG or monoclonal antibodies. The downfall is that it has however been linked to several skin reactions, infections and severe allergic reactions(Reisacher and FAAOA).

Ligand-targeted therapy on the other hand, involves using the genes of a patient, their proteins and cancer features to treat the cancer, it has two main difficulties when it comes to implementation of the treatment. One is that cancer cells become resistant and two, drugs for some targets are hard to design (Wu *et al.*, 2006) .

Hormone/hormonal therapy either slows down or stops the growth of cancers sentient to the endocrine like breast cancer. (Byar and Corle, 1988; Zelnak and Carthon, 2018). Treatment involves withdrawing the growth stimulus either by slowing down the rate at which hormones are generated or by obstructing the attachment of receptors and ligands (Jones *et al.*, 2004).

Stem cell transplants procedures aid in restoring blood-forming stem cells in patients who have already gone through chemotherapy and radiotherapy. This treatment may carry with it heavy bleeding and subsequently, a very high risk of infection. It is also quite expensive (Reya *et al.*, 2001).

Whilst these various treatments have been administered to patients over the years, they are not 100% successful and therefore the need to sought a much better treatment method. This search is what has led to interest in virotherapy.

Due to more advanced studies in genetic engineering from that time on and especially in recent years, replication-competent viruses are now being used as a selective mode of cancer therapy (Rajalakshmi and Ghosh, 2018; Ring, 2002). Viruses are known to

have cytotoxic effects (can be toxic to cells). Advancements in science has aimed at harnessing these effects to target cancer cells. This is because viral genomes are highly versatile therefore easily modified by either selectively infecting or replicating in cancer cells. The viruses herein referred, are known as **Oncolytic Viruses** (Berkey *et al.*, 2017; Chiocca, 2002). These viruses with tumor specificity date back to the *1950s* and *1960s* as being experimentally researched on but there was very limited success which forced researches to abandon their study within a decade. Recent advancement in science and technology has seen the resurgence of their study and keen interest in their specificity to liase only tumor cells leaving healthy cells unharmed. In 2005, Chinese regulators announced a market approval for the first ever oncolytic virus, which was the adenovirus H101 (Garber, 2006; Kelly and Russell, 2007).

Viruses being developed include herpes simplex, adeno, Newcastle disease viruses,weasles among others (Ring, 2002). Tests have been carried out in animal studies yielding encouraging results and consequently, some viruses are on clinical trials (Ring, 2002).

In as much as this new viral treatment approach has several potential attributes, it also carries with it a number of other several potential disadvantages like tumor cells impervious to viral treatment (Vähä-Koskela *et al.*, 2007), all which need to be addressed (Kirn and McCormick, 1996).

These viruses destroy the cancer tumor cells in two main ways :

a) by being directly cytolytic to the host tumor cells which in turn may lead to to tumor remission (Wodarz, 2001) or

b) specific immune responces may be induced due to the presence of the virus leading to lysis of the tumor cells (Wodarz, 2001)

The agency for research on cancer (International agency for research on Cancer, 2018) responsible of collecting worldwide data, highlights that cancer is a huge societal burden and has become a major focus in finding ways on how best to mitigate this disease listed among non-communicable diseases (NCDs)

According to the World Cancer Research Fund (World Cancer Research Foundation, 2018), in 2018, it was projected that the most common type of cancers worldwide were lung and breast cancer, accounting for $\sim$ 12.3% each of the total new diagnosed cases. In

men, $\sim$ 44.4% of all cancers were lung, prostate and colorectal cancers and their prevalence was in the same order. In their female counterparts, the most common types in order were breast, colorectal and lung cancers with breast cancer contributing $\sim$ 25.4% of the overall $\sim$ 43.9%. All the cases excluded non-melanoma skin cancer. More clearly, $\sim$ 18 million cancer cases were diagnosed with 9.5 million cases reported in men and the remaining 8.5 million in women.

2.3 Summary

Having discussed what cancer is, its causes, stages, treatment methods available as well as the groups in which different cancer falls, we introduced the new realm of treatment known as Oncolytic virotherapy where the normal cells are left unharmed.

Chapter 3

Preliminaries on Delay Differential Equations

We table a few preliminary findings on delay differential equations from the book Erbe (2017), that we need throughout this thesis.

3.0.1 Existence and Uniqueness Results

Let τ be a positive constant and denote by $C = C([-\tau, 0], \mathbb{R}^n)$ the Banach space of continuous functions defined on the interval $[-\tau, 0]$ into $\mathbb{R}^n$ endowed with norm

$$\|\varphi\| = \sup_{\theta \in [-\tau, 0]} \|\varphi(\theta)\|, \varphi \in C$$

Let α be a real positive number and x an element of $C([-\tau, \alpha], \mathbb{R}^n)$ For all $t \in [0, \alpha]$, we denote by x_t the function (in C) defined by

$$x_t(\theta) = x(t + \theta), \theta \in [-\tau, 0].$$

Let f be a function defined on an open subset Ω of C with values in $\mathbb{R}^n$ and consider the following delay differential equation:

$$\frac{d}{dt}x(t) = f(x_t), \text{ for all } t \geq 0 \tag{3.0.1}$$

Definition 3.0.1. *The function $f : C \to \mathbb{R}^n$ is differentiable at ϕ, if there exists a linear function L_ϕ such that*

$$f(\phi + \psi) = f(\phi) + L_\phi(\psi) + \varepsilon(\|\psi\|),$$

where ε satisfies the condition $\lim_{\|\psi\| \to 0} \frac{\varepsilon(\|\psi\|)}{\|\psi\|} = 0$
We denote $D_\varphi f(\phi)\psi = L_\phi(\psi)$, where the subscript ϕ is omitted for notation convenience.

Lemma 3.0.2. *For each constant $c \in [-\tau, 0]$, the function $g : C \to \mathbb{R}$ defined by*

$$g(\phi) = \phi(c)$$

is differentiable and

$$D_\varphi g(\phi)\psi = \psi(c)$$

Proof. We have

$$g(\phi+\psi) - g(\phi) = (\phi+\psi)(c) - \phi(c) = \phi(c) + \psi(c) - \phi(c) = \psi(c) = \psi(c).$$

Then

$$g(\phi+\psi) = g(\phi) + \psi(c)$$

which we write as

$$g(\phi+\psi) = g(\phi) + L_\phi(\psi) + \varepsilon(\|\psi\|)$$

where $L_\phi(\psi) = \psi(c)$ and $\varepsilon(\|\psi\|) = 0$ which satisfies $\lim_{\|\psi\|\to 0} \frac{\varepsilon(\|\psi\|)}{\|\psi\|} = 0$
Hence $D_\varphi g(\phi)\psi = \psi(c)$ □

Using the lemma above and the product rule for derivatives we obtain the following lemma:

Lemma 3.0.3. *For each constant $c \in [-\tau, 0]$, the function $g : C([-\tau, 0], \mathbb{R}^2) \to \mathbb{R}^2$ defined by*

$$g(\phi) = \phi_1(c)\phi_2(c)$$

is differentiable and

$$D_\varphi g(\phi)\psi = \psi_1(c)\phi_2(c) + \phi_1(c)\psi_2(c).$$

Proof. We have

$$\begin{aligned} g(\phi+\psi) - g(\phi) &= (\phi_1+\psi_1)(c)(\phi_2+\psi_2)(c) - \phi_1(c)\phi_2(c) \\ &= \phi_1(c)\psi_2(c) + \psi_1(c)\phi_2(c) + \psi_1(c)\psi_2(c), \end{aligned}$$

which we write as

$$g(\phi+\psi) = g(\phi) + L_\phi(\psi) + \varepsilon(\|\psi\|)$$

where

$$L_\phi(\psi) = \phi_1(c)\psi_2(c) + \psi_1(c)\phi_2(c)$$

and

$$\varepsilon\left(\|\psi\|\right) = \psi_1\left(c\right)\psi_2\left(c\right)$$

which satisfies $\lim_{\|\psi\|\to 0} \frac{\varepsilon(\|\psi\|)}{\|\psi\|} = 0$.
Hence

$$D_{\varphi}g\left(\phi\right)\psi = \phi_1\left(c\right)\psi_2\left(c\right) + \psi_1\left(c\right)\phi_2\left(c\right)$$

□

Definition 3.0.4. *Let φ be an element of C. A function x is a solution of equation (3.0.1) with initial value φ at $t = 0$, if there exists a constant $\alpha > 0$ such that:*

i. *x is defined and continuous on the interval $[-\tau, \alpha]$;*

ii. *$x_0 = \varphi$;*

iii. *x is differentiable on $[0, \alpha]$ and satisfies the equation (3.0.1) for all $t \in [0, \alpha]$.*

The following theorem guaranties the existence and uniqueness of solutions for equation (3.0.1):

Theorem 3.0.5. *Let Ω be an open subset of C and f be a function defined on an open subset Ω. If f is continuous, then equation (3.0.1) has for each element φ in C, at least one solution with initial condition φ. If, in addition, the function f is locally Lipschitzian, then the solution is unique.*

For the global existence of solutions we refer to the following proposition:

Theorem 3.0.6. *Assume that for some constants $c_1, c_2 \geq 0$ the function f is continuous and satisfies the condition*

$$\|f(\varphi)\| \leq c_1 \|\varphi\| + c_2,\ \varphi \in C.$$

Then, for all φ in C, the solution of equation (3.0.1) with initial condition φ is defined on the entire interval $[-\tau, +\infty]$.

3.0.2 Equilibria and Stability

Consider the following linear equation

$$\frac{d}{dt}x(t) = Lx_t, \tag{3.0.2}$$

where L is a continuous linear operator from C into $\mathbb{R}^n$.

Definition 3.0.7. *The characteristic equation associated with equation (3.0.2) is obtained by exploring solutions of (3.0.2) of the form $x(t) = e^{zt}$. It is given by*

$$\det \Delta(z) = 0, \tag{3.0.3}$$

where $\Delta(z) = zI_{n\times n} - L(e^{z\cdot}I_n)$, with $I_{n\times n}$ denoting the $n \times n$ matrix, I_n is the vector $\begin{bmatrix} 1 \\ \vdots \\ 1 \end{bmatrix}$ *and $e^{z\cdot}I_n$ being the function defined by:*

$$\theta \in [-\tau, 0] \mapsto e^{z\theta}I_n = \begin{bmatrix} e^{z\theta} \\ \vdots \\ e^{z\theta} \end{bmatrix}$$

In the remainder of this chapter we drop the subscripts and denote both $I_{n\times n}$ and I_n by I.

Theorem 3.0.8.

1. *If all the roots of (3.0.3) have negative real parts, then the trivial solution $x \equiv 0$ for equation (3.0.2) is exponentially asymptotically stable.*
2. *If at least one of the roots of (3.0.3) has a positive real part, then $x \equiv 0$ is unstable.*

Consider the 'semi-linear' equation

$$\frac{d}{dt}x(t) = Lx_t + F(x_t), \tag{3.0.4}$$

where F is continuously differentiable on C with values in $\mathbb{R}^n$ such that $F(0) = 0$ and $D_\varphi F(0) = 0$. The characteristic equation of (3.0.4) at $x \equiv 0$ is given by

$$\det\left(zI - L(e^{z\cdot}I)\right) = 0. \tag{3.0.5}$$

It results in:

Theorem 3.0.9. *1. If all the roots of (3.0.5) have negative real parts, then the equilibrium solution $x \equiv 0$ for equation (3.0.4) is asymptotically stable.*

2. If at least one of the roots of (3.0.5) has a positive real part, then $x \equiv 0$ is unstable.

Assume now that equation (3.0.1) has an equilibrium point, x^*, i.e. $f(x^*) = 0$, and that f is continuously differentiable. The characteristic equation of (3.0.4) at x^* is given by

$$\det\left(zI - L(e^{z\cdot}I)\right) = 0, \tag{3.0.6}$$

where $L(\psi) = D_\varphi f(x^*)\psi$.
By a simple change of variable, $y(t) = x(t) - x^*$, which shifts the equilibrium point x^* to 0, we deduce from Theorem (3.0.9) the following result:

Theorem 3.0.10. *1. If all the roots of (3.0.6) have negative real parts, it follows that the equilibrium solution $x \equiv x^*$ for equation (3.0.1) is asymptotically stable.*

2. If at least one of the roots of (3.0.6) has a positive real part, then $x \equiv x^*$ is unstable.

3.0.2.1 Example 1

Consider the following equation:

$$\frac{dx}{dt} = ax(t) + bx(t-\tau)$$

Using the shift notation $y_t(\theta) = y(t+\theta)$, the above equation becomes

$$\frac{dx}{dt} = ax_t(0) + bx_t(-\tau)$$

which we can further write as

$$\frac{dx}{dt} = f(x_t)$$

where $f : C = C([-\tau, 0], \mathbb{R}) \to \mathbb{R}$ is defined by

$$f(\phi) = a\phi(0) + b\phi(-\tau).$$

Using Lemma 3.0.2, we deduce that the derivative of the function $f(\phi) = a\phi(0) + b\phi(-\tau)$ at ϕ is given by

$$L\psi = D_\varphi f(\phi)\psi = a\psi(0) + b\psi(-\tau).$$

The characteristic equation is given by

$$\det\left(zI - L\left(e^{z\cdot}I\right)\right) = 0$$

that is

$$\begin{aligned} z - a\left(e^{z\cdot}I\right)(0) - b\left(e^{z\cdot}I\right)(-\tau) &= 0 \\ z - a - be^{-z\tau} &= 0 \end{aligned}$$

3.0.2.2 Example 2

Consider the following basic model for virotherapy

$$\begin{cases} \dfrac{dS}{dt} = \lambda - dS - \beta SV \\ \dfrac{dI}{dt} = \beta SV - \delta I \\ \dfrac{dV}{dt} = N\delta I - cV. \end{cases} \tag{3.0.7}$$

Full details of the meaning and assumptions of this model are presented in Chapter 3. Introducing a constant delay τ (accounting for the duration of time required for replication of infected cells), we obtain the following model

$$\begin{cases} \dfrac{dS}{dt} = \lambda - dS - \beta SV \\ \dfrac{dI}{dt} = \beta S\left(t-\tau\right)V\left(t-\tau\right) - \delta I \\ \dfrac{dV}{dt} = N\delta I - cV \end{cases} \tag{3.0.8}$$

To study this model we first write it into the standard from (3.0.1).

Define the set $C = C\left(\left[-\tau, 0\right], \mathbb{R}^3\right)$ and let $x\left(t\right) = \begin{bmatrix} S\left(t\right) \\ I\left(t\right) \\ V\left(t\right) \end{bmatrix}$, then model (3.0.8) reads as

$$\frac{dx}{dt} = \begin{bmatrix} \lambda - dx_1\left(t\right) - \beta x_1\left(t\right)x_3\left(t\right) \\ \beta x_1\left(t-\tau\right)x_3\left(t-\tau\right) - \delta x_2\left(t\right) \\ N\delta x_2\left(t\right) - cx_3\left(t\right) \end{bmatrix}$$

Using the shift notation $y_t\left(\theta\right) = y\left(t+\theta\right)$, the above equation becomes

$$\frac{dx}{dt} = \begin{bmatrix} \lambda - dx_{t_1}\left(0\right) - \beta x_{t_1}\left(0\right)x_{t_3}\left(0\right) \\ \beta x_{t_1}\left(-\tau\right)x_{t_3}\left(-\tau\right) - \delta x_{t_2}\left(0\right) \\ N\delta x_{t_2}\left(0\right) - cx_{t_3}\left(0\right) \end{bmatrix}$$

which we can further write as

$$\frac{dx}{dt} = f\left(x_t\right)$$

where $f : C = C\left(\left[-\tau, 0\right], \mathbb{R}^3\right) \to \mathbb{R}^3$ is given by

$$f\left(\phi\right) = \begin{bmatrix} \lambda - d\phi_1\left(0\right) - \beta\phi_1\left(0\right)\phi_3\left(0\right) \\ \beta\phi_1\left(-\tau\right)\phi_3\left(-\tau\right) - \delta\phi_2\left(0\right) \\ N\delta\phi_2\left(0\right) - c\phi_3\left(0\right) \end{bmatrix}$$

Lemma 3.0.11. *The characteristic equation of model (3.0.8) at an equilibrium point $E = (S, I, V)$ is given by*

$$\chi_E = \det\begin{pmatrix} -d - \beta V - z & -rkS & -\beta S \\ \beta e^{-z\tau_1} V & -\delta - z & \beta e^{-z\tau_1} S \\ 0 & p & -c - z \end{pmatrix} = 0$$

Proof. The characteristic equation of model (3.0.8) at $E = (S, I, V)$ is given by

$$\det\left(zI - L(e^{z\cdot} I)\right) = 0,$$

where $L\left(\psi\right) = D_\varphi f\left(E\right)\psi$ is calculated using Lemmas (3.0.2) and (3.0.3). We obtain

$$Df\left(E\right)\phi = \begin{bmatrix} -d\phi_1\left(0\right) - \beta\phi_1\left(0\right)V & 0 & -\beta S\phi_3\left(0\right) \\ \beta\phi_1\left(-\tau\right)V & -\delta\phi_2\left(0\right) & \beta S\phi_3\left(-\tau\right) \\ 0 & N\delta\phi_2\left(0\right) & -c\phi_3\left(0\right) \end{bmatrix}$$

Then

$$Df\left(E\right)\left(e^{z\cdot} I\right) = \begin{bmatrix} -d - \beta V & 0 & -\beta S \\ \beta e^{-z\tau_1} V & -\delta & \beta S e^{-z\tau_1} \\ 0 & N & -c \end{bmatrix}$$

Thus

$$det(zI - L(e^z I)) = \begin{bmatrix} z + d + \beta V & 0 & \beta S \\ -\beta e^{-z\tau_1} V & z + \delta & -\beta S e^{-z\tau_1} \\ 0 & -N & z + c \end{bmatrix} = 0$$

□

Chapter 4

Overview of simple mathematical models of tumor virotherapy

4.1 Introduction

We now assess some basic models of tumor oncolytic virotherapy (Russell *et al.*, 2012),(Liu *et al.*, 2007) and (Vile *et al.*, 2002), followed by a preliminary analysis of their qualitative properties. We further carry out mathematical analysis of their equilibria and apply the next generation matrix determining the reproductive number $\mathcal{R}_0$ and later analyse the sensitivity indices. We end the chapter by a discussion of a model by (Bajzer *et al.*, 2008)

4.2 Overview of a simple virotherapy model

A simple representation of models proposed in (Russell *et al.*, 2012),(Liu *et al.*, 2007),(Vile *et al.*, 2002) and (Bajzer *et al.*, 2008) can be formulated as follows

$$\begin{cases} \frac{dS}{dt} = \lambda - dS - \beta SV \\ \frac{dI}{dt} = \beta SV - \delta I \\ \frac{dV}{dt} = N\delta I - cV \end{cases} \tag{4.2.1}$$

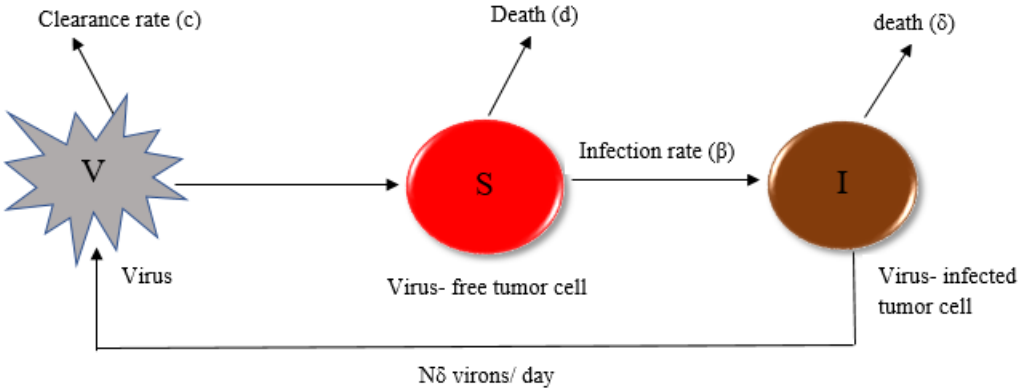


Figure 4.1: Basic Viral Infection Model

Here S represents uninfected tumor cells which are assumed to grow at a constant rate λ, then either die with a per capita constant rate d or get infected with oncolytic virus at a constant rate β.

Cells that have been infected, I, perish via natural process or when they burst at a constant rate δ (higher than that of the uninfected cells i.e. $\delta > d$). We presume the (natural) death rate is negligible in contrast to the bursting rate and therefore, throughout this thesis, we will refer to the latter as the death rate. Tumor cells that burst produce N viruses which will either be cleared at a rate c or proceed to infect other cells within the population. (Dingli *et al.*, 2006)

In the investigation of the oncolytic effect, the key parameters we will be keenly looking at include the infection rate β, the life span of the contaminated cells δ, in addition to the rate at which the virus is cleared, c and the burst size N. We need to figure out which among these parameters is key in increasing and perhaps maximizing the effect of the oncolytic viruses. β would be of importance since the oncolytic viruses are capable of infecting a large number of tumor cells. N is also important because tumor cells that are infected with oncolytic viruses have a high number of infected cases spawned from each infected case. Clearance rate c is also key because once the viruses have been intravenously introduced into the host, they need to atleast live until they reach the target cells and not die immediately due to a harsh environment. Even when produced, they manage to infect some cells and then consequently those cells manage to produce

some viruses N.

In the next subsection, we will calculate the basic reproductive number ($\mathcal{R}_0$) which summarises the combined effect of the above parameters on viral replication and consequently, tumor reduction. We will calculate $\mathcal{R}_0$ and investigate its sensitivity with respect to these parameters.

The basic reproduction number has been used in epidemiology at population level for diseases such as TB (Blower *et al.*, 1995) and HIV (Ribeiro *et al.*, 2010) as well as within host models with cellular growth. (Hassell and May, 1973; Li and Shu, 2010). Typically, we witness an outbreak of an epidemic when $\mathcal{R}_0 > 1$, whereas the illness may wash away should $\mathcal{R}_0 < 1$. Consequently, the value of the reproductive number would thus be crucial in determining how to slow down the effects of an epidemic or further to entirely suppress an infection in a given population.

We note here that models of this type have been studied to model the interaction between HIV and the immunity whereby S would be the T-cells population; I the number of adequately infected cells and V is the number of loose virus (Chun *et al.*, 1997; Nowak and Bangham, 1996; Rouzine and Weinberger, 2013; Stafford *et al.*, 2000; Tuckwell and Shipman, 2011)

We calculate the basic reproductive number ($\mathcal{R}_0$) which is detailed as the average amount of secondary (viral) infection emerging from one infected (tumor) cell in a completely vulnerable population during its whole infectious span.

4.2.1 Next Generation Method

The next generation technique was introduced by Van den Driessche and Watmough (Van den Driessche and Watmough, 2002) to calculate the basic reproductive number. A brief description of this method is as follows:
Assume that a population $x = (x_1, \cdots, x_n)$ that is subject to a disease is modelled by this system of ordinary differential equations

$$\frac{dx_i}{dt} = \mathcal{F}_i(x) - \mathcal{V}_i(x),\ i = 1, \cdots, n$$

where $x_i, i = 1, ..., m$ represent the infected population, while $x_i, i = m+1, ..., n$ represent individuals susceptible to infection. $\mathcal{F}_i(x)$ is the frequency of occurrence of newer infections within compartment i and $\mathcal{V}_i(x) = \mathcal{V}_i^-(x) - \mathcal{V}_i^+(x)$ with $\mathcal{V}_i^+(x)$ (resp. $\mathcal{V}_i^-(x)$) as the occurrence of new entities into (resp. out of) partition i by other means.

We further assume that the disease-free state set, denoted by X_s, is non-empty and that the three functions $\mathcal{F}_i$, $\mathcal{V}_i^-$ and $\mathcal{V}_i^+$ are presumed to be continuously differentiable and satisfy the list below:

1. If $x \geq 0$, then $\mathcal{F}_i, \mathcal{V}_i^+, \mathcal{V}_i^- \geq 0$ for $i = 1, ..., n$.
2. If $x_i = 0$, then $\mathcal{V}_i^- = 0$, particularly, if $x \in X_s$, then, $\mathcal{V}_i^- = 0$ for $i = 1, ..., m$.
3. $\mathcal{F}_i = 0$ if $i > m$.
4. If $x \in X_s$, then, $\mathcal{F}_i(x) = 0$ and $\mathcal{V}_i^+(x) = 0$ for $i = 1, ..., m$.

   We further assume that the model has an asymptotically stable disease-free equilibrium x_0.
5. If $F\mathcal{F}(x)$ is fixed at null, then all the eigenvalues of $D\mathcal{F}(x_0)$ have non-positive real parts.

The basic reproductive number is prescribed as

$$\mathcal{R}_0 = \rho\left(D\mathcal{F}(x_0)\left[D\mathcal{V}(x_0)\right]^{-1}\right)$$

where $\rho(M)$ is the spectral radius of the matrix M, that is, $\max_{z\in\sigma(M)} |z|$ where $\sigma(M)$ is the set of all eigenvalues of M.
The matrix

$$M = D\mathcal{F}(x_0)\left[D\mathcal{V}(x_0)\right]^{-1}$$

is called the next generation matrix.

Concerning model (4.2.1), we first sort the equations so that the first equations are for the infected classes, obtaining

$$\begin{cases} \dfrac{dI}{dt} = \beta SV - \delta I \\ \dfrac{dV}{dt} = N\delta I - cV \\ \dfrac{dS}{dt} = \lambda - dS - \beta SV \end{cases}$$

The disease-free equilibrium of the (sorted) model is given by $x_0 = (0, 0, S_0)$, where $S_0 = \frac{\lambda}{d}$. The rate of new infections is $\mathcal{F} = \begin{bmatrix} \beta SV \\ 0 \end{bmatrix}$ and that of other transfers is given

by $\mathcal{V} = \begin{bmatrix} \delta I \\ -N\delta I + cV \end{bmatrix}$.
The next generation matrix is given by

$$\begin{aligned} DF(x_0)\left[D\mathcal{V}(x_0)\right]^{-1} &= \begin{bmatrix} 0 & \beta S_0 \\ 0 & 0 \end{bmatrix} \begin{bmatrix} \delta & 0 \\ -N\delta & c \end{bmatrix}^{-1} \\ &= \begin{bmatrix} \frac{N}{c}\beta S_0 & \frac{1}{c}\beta S_0 \\ 0 & 0 \end{bmatrix} \end{aligned}$$

(where S_0 is the initial tumor size)

The basic reproductive number is then

$$\mathcal{R}_0 = \rho\left(D\mathcal{F}(x_0)\left[D\mathcal{V}(x_0)\right]^{-1}\right) = \rho\left(\begin{bmatrix} \frac{N}{c}\beta S_0 & \frac{1}{c}\beta S_0 \\ 0 & 0 \end{bmatrix}\right)$$

Finally, we obtain

$$\mathcal{R}_0 = \frac{\beta\lambda N}{cd}.$$

4.2.2 Sensitivity Index of $\mathcal{R}_0$

In general, sensitivity analysis can be used to measure different reaction of precariousness of the loaded parameters of a model and subsequently, the effect(s) on the model's output. This basically means that sensitivity analysis of a model may showcase how much input variability there is which may consequently cause variations in the model products. In other words, the main motive of this analysis is to quantify this input-output relationship. This analysis may be applied in refining mathematical models through quantitatively showcasing major features and methods that can sometimes steer towards identifying approaches to be used for lowering the prospect of disease spread in a population, in our case, tumor cells population. (Arriola and Hyman, 2009)

Since $\mathcal{R}_0$ depends on factors such as timespan of infection, rate of infecting a susceptible cell as well as the quantity of new viruses induced by an infected cell 1% variations in different parameters may therefore cause different variations in $\mathcal{R}_0$.

In this section, we seek to find out how sensitive $\mathcal{R}_0$ is to some of the model's parameters, this will further show the relative significance of the parameters on the model forecasts herewith.

Generally, sensitivity index is defined as the proportion of the relative change in a given variable to that in the parameter (Chitnis *et al.*, 2013). We may use partial derivatives to compute it when the variable is a differentiable function of the parameter .

Definition 4.2.1. *(Romoser* et al., *2011)The sensitivity index of a variable ξ with respect to a parameter p*

$$\Gamma_{\xi}^{p} = \frac{\partial \xi}{\partial p}\frac{p}{\xi}.$$

We can see from the formula that if $\Gamma_{p}^{\xi} = \alpha$, then,

$$\frac{\Delta \xi}{\xi} \approx \alpha \frac{\Delta p}{p}$$

This implies that when $\frac{\Delta p}{p} = 1\%$, then $\frac{\Delta \xi}{\xi} \approx \alpha\%$. This means that a proportional increase of 1% in p, translates to an increase of α% in ξ (α may be positive or negative).

Lemma 4.2.2. *The sensitivity index of any variable of the form $\xi = qp^r$, is given by*

$$\Gamma_{\xi}^{p} = r.$$

Proof. We have

$$\Gamma_{\xi}^{p} = \frac{\partial \xi}{\partial p}\frac{p}{\xi} = rqp^{r-1}\frac{p}{qp^r} = r.$$

□

Applying the lemma above to $\mathcal{R}_0$, we obtain

$$\begin{cases} \Gamma_{\mathcal{R}_0}^{c} = -1 \\ \Gamma_{\mathcal{R}_0}^{\beta} = \Gamma_{\mathcal{R}_0}^{N} = 1. \end{cases}$$

We can now deduce that the reproductive number, $\mathcal{R}_0$, is sensitive in absolute value, equally to all parameters β, c and N. In fact 1% decrease in c (resp. increase in β or N) will lead to 1% increase (resp. decrease) in $\mathcal{R}_0$. Our aim is to increase $\mathcal{R}_0$. We can achieve this either by increasing β or N or by decreasing c.

Calculating $\mathcal{R}_0$ and assessing its sensitivity is useful in informing us if viral infection will persist or die out, however, it does not inform us on the transient and equilibrium stages and how sensitive they are to the relevant parameters. Therefore, we seek in

the next section to calculate the equilibrium points and investigate their sensitivity to the key virus parameters. Numerical simulations can be performed to investigate the intermediate stages and confirm the mathematical findings. This will be done for the more general model that we will be dealing with in Chapter 5.

4.2.3 Equilibrium points and stability

We evaluate the system below to achieve the equilibrium points

$$\begin{cases} \lambda - dS - \beta SV = 0 \\ \beta SV - \delta I = 0 \\ N\delta I - cV = 0 \end{cases} \tag{4.2.2}$$

Equation (4.2.2)$_3$ implies that $I = \frac{cV}{N\delta}$. Substituting this in equation (4.2.2)$_2$ leads to

$$V\left(\beta S - \frac{c}{N}\right) = 0.$$

Hence $V = 0$, leading the virus free equilibrium $VFE = \left(\frac{\lambda}{d}, 0, 0\right)$, or $S = \frac{c}{N\beta}$, leading the the virus infected equilibrium

$$\begin{aligned} VIE &= \left(\frac{c}{N\beta}, \frac{cd}{N\delta\beta}\left(\mathcal{R}_0 - 1\right), \frac{d}{\beta}\left(\mathcal{R}_0 - 1\right)\right) \\ &= \left(\frac{S_0}{\mathcal{R}_0}, \frac{\lambda}{\delta}\left(1 - \frac{1}{\mathcal{R}_0}\right), \frac{\lambda N}{c}\left(1 - \frac{1}{\mathcal{R}_0}\right)\right). \end{aligned}$$

VIE is biologically feasible if and only if $\mathcal{R}_0 > 1$, in the next theorem, we establish its stability properties.

Theorem 4.2.3. *When $\mathcal{R}_0 < 1$, VFE is the model's (4.2.1) sole equilibrium point and is locally asymptotically stable. When $\mathcal{R}_0 > 1$, VFE becomes not stable and VIE exists and is locally asymptotically stable.*

Proof. Existence of equilibrium points has already been discussed in the beginning of this section. The stability properties of an equilibrium point $E = (S, I, V)$ are found from the Jacobian matrix through calculation of eigenvalues

$$J_E = \begin{bmatrix} -d - \beta V & 0 & -\beta S \\ \beta V & -\delta & \beta S \\ 0 & N\delta & -c \end{bmatrix}.$$

- At VFE, we have
$$J_{VFE} = \begin{bmatrix} -d & 0 & -\frac{\beta\lambda}{d} \\ 0 & -\delta & \frac{\beta\lambda}{d} \\ 0 & N\delta & -c \end{bmatrix}$$
whose eigenvalues are awarded by roots of the characteristic polynomial
$$(X+d)\left(X^2 + X(\delta+c) + c\delta(1-\mathcal{R}_0)\right) = 0.$$
Hence VFE is locally asymptotically stable if and only if $\mathcal{R}_0 < 1$.

- At VIE, we have
$$J_{VIE} = \begin{bmatrix} -d-\beta V & 0 & -\beta S \\ \beta V & -\delta & \beta S \\ 0 & N\delta & -c \end{bmatrix}$$
with characteristic polynomial,
$$\chi = X^3 + A_2X^2 + A_1X + A_0$$
where
$$\begin{aligned} A_0 &= \delta(cd + Vc\beta - NSd\beta) \\ A_1 &= (\delta(d+V\beta) + c(d+\delta+V\beta) - NS\beta\delta) \\ A_2 &= (c+d+\delta+V\beta). \end{aligned}$$
Since $S = \frac{c}{N\beta}$, then
$$\begin{aligned} A_0 &= \delta c\beta V \\ A_1 &= \delta(d+V\beta) + c(d+\delta+V\beta) - c\delta = (c+\delta)(d+V\beta). \end{aligned}$$
If $\mathcal{R}_0 > 1$, then $V > 0$ implying that A_0, A_1 and A_1 are all positive. Moreover,
$$A_1A_2 - A_0 = (c+\delta)(d+V\beta)(c+d+\delta+V\beta) - \delta c\beta V > 0.$$
Then by Routh-Hurwitz criterion all roots of the characteristic polynomial χ have negative real parts, implying the VIE is locally asymptotically stable.

□

Next, we investigate how/if virotherapy helps reduce the Total Tumor Size at the virus infected equilibrium. TTS is given by

$$TTS = \frac{S_0}{\mathcal{R}_0} + \frac{\lambda}{\delta}\left(1 - \frac{1}{\mathcal{R}_0}\right).$$

calculated from adding both the uninfected and infected tumor populations from the VIE.

Proposition 4.2.4. *If $\mathcal{R}_0 > 1$ then $TTS < S_0$ if and only if $\delta > d$.*

Proof. The total tumor population at equilibrium is given by

$$\begin{aligned} TTS &= \frac{S_0}{\mathcal{R}_0} + \frac{d}{\delta} S_0 \left(1 - \frac{1}{\mathcal{R}_0}\right) \\ &= S_0 \left(\frac{1}{\mathcal{R}_0} + \frac{d}{\delta} - \frac{d}{\delta}\frac{1}{\mathcal{R}_0}\right) \end{aligned}$$

Hence, the reduction in tumor size is given by

$$\begin{aligned} TTS - S_0 &= S_0 \left(\frac{1}{\mathcal{R}_0} - \frac{d}{\delta}\frac{1}{\mathcal{R}_0} + \frac{d}{\delta} - 1\right) \\ &= S_0 \left(\frac{1}{\mathcal{R}_0}\left(1 - \frac{d}{\delta}\right) + \frac{d}{\delta} - 1\right) \\ &= S_0 \left(1 - \frac{d}{\delta}\right)\left(\frac{1}{\mathcal{R}_0} - 1\right). \end{aligned}$$

Thus, $TTS < S_0$ if and only if $R_0 > 1$ and $\delta > d$. □

The proposition above clearly shows that virotherapy helps reduce the total tumor size (at equilibrium) as long as the oncolytic virus used has a basic reproductive number that is higher than one and induces a mortality rate (of cells that have been infected) which is greater than that of those uninfected ($\delta > d$).

Noting the expression $\mathcal{R}_0 = \frac{\beta\lambda N}{cd}$ does not involve infected tumor cells' mortality rate δ (which is substantially higher than speed of mortality of uninfected cancerous cells), we deduce that one can increase the oncolytic effect in two independent ways:

1. Increasing δ, this would achieve a minimum tumor size equal to

$$TTS_1 = \frac{S_0}{\mathcal{R}_0}.$$

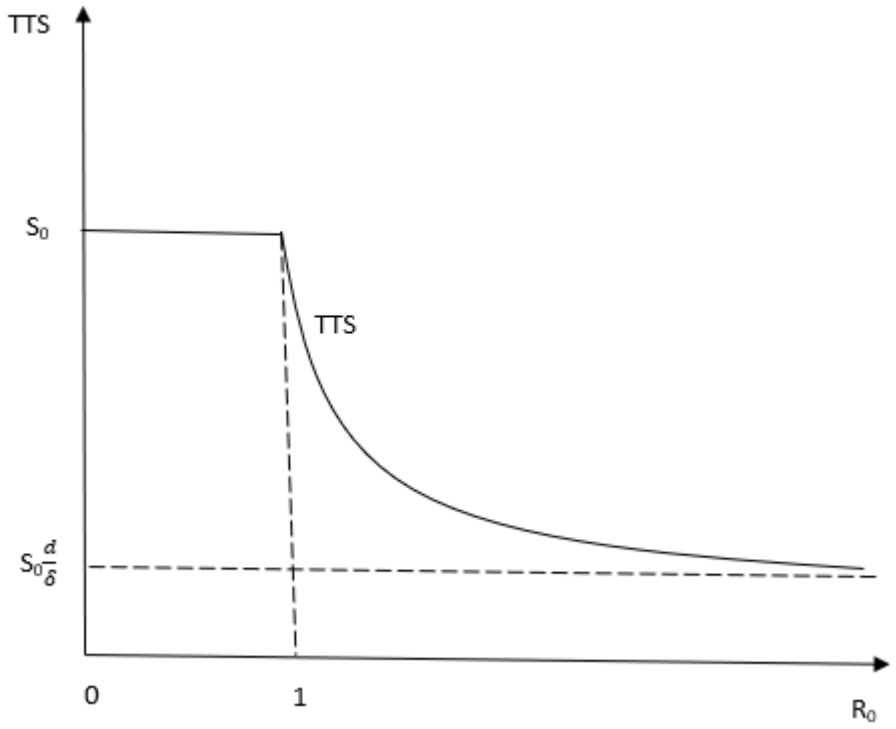


Figure 4.2: Bifurcation Diagram 1

2. Alternatively, one can also increase $\mathcal{R}_0$, which (by the sensitivity index analysis of $\mathcal{R}_0$ performed in the previous section) can be **equally** achieved by increasing β (or N) or decreasing c (λ and d being tumor parameters are left fixed). By rewriting the formula of TTS as

$$TTS = S_0 \left(\frac{1}{\mathcal{R}_0} \left(1 - \frac{d}{\delta} \right) + \frac{d}{\delta} \right)$$

we find that the minimal tumor size achieved is

$$TTS_2 = \frac{d}{\delta} S_0$$

3. Tumor "elimination" would be achieved if we simultaneously increase δ and $\mathcal{R}_0$, then the minimal tumor size achieved is 0.

See the bifurcation diagram above for a graphical interpretation of the above points.

The proposition further shows how the proportional reduction in tumor size changes with $\mathcal{R}_0$ (and/or δ). In fact,

$$\frac{TTS - S_0}{S_0} = \left(1 - \frac{d}{\delta}\right)\left(\frac{1}{\mathcal{R}_0} - 1\right)$$

Which demonstrates a proportional decrease in the total tumor size that is linear with respect to $\frac{1}{\mathcal{R}_0}$ and/or $\frac{1}{\delta}$.

To investigate which of the of the virus parameters contributes most to the reduction of the total tumor size, we perform in the next section, a sensitivity analysis of TTS in respect of virus parameters and death rate of the contaminated cells.

4.2.4 Sensitivity index of the endemic equilibrium point

Using the expression of the total tumor size at equilibrium

$$TTS = \frac{\lambda}{d}\left(\frac{cd}{\beta\lambda N}\left(1 - \frac{d}{\delta}\right) + \frac{d}{\delta}\right)$$

Using the programming software, SAGEMATH, we calculate the formula of the sensitivity index of TTS and obtain

$$\begin{cases} \Gamma^{\delta}_{TTS} = \dfrac{dc - \lambda\beta N}{c\delta + \lambda\beta N - dc} \\ \Gamma^{c}_{TTS} = \dfrac{c(\delta - d)}{c\delta + \lambda\beta N - dc} \\ \Gamma^{N}_{TTS} = \dfrac{c(d - \delta)}{c\delta + \lambda\beta N - dc} \\ \Gamma^{\beta}_{TTS} = \dfrac{c(d - \delta)}{c\delta + \lambda\beta N - dc} \end{cases}$$

We note that $\Gamma^{\beta}_{TTS} = \Gamma^{N}_{TTS} = -\Gamma^{c}_{TTS}$ which means in absolute values, all three parameters have the same proportional effect on TTS.

Now we use parameter values from table (4.1) to evaluate the sensitivity index of TTS with respect to δ and β.

We note that the value of λ can be derived from the relation $\lambda = S_0 d$. If we consider a tumor of size 2cm in diameter which is roughly 10^8 cells, then using the value of $d = 0.001$ given in Table 4.1, we obtain $\lambda = 10^5$. N is chosen to be equal to 3000.

parameter	definition	value	Source
r	growth rate of uninfected tumor cells	$2 * 10^{-2}$	(Okamoto *et al.*, 2014)
k	carrying capacity	0.000467	(Mahasa *et al.*, 2017)
δ	death rate of uninfected tumor cells	$\frac{1}{18}$	(Malinzi *et al.*, 2018)
γ	virus elimination rate	$2 * 10^{-8}$	(Malinzi *et al.*, 2018)
p	virus production rate	0.001	(Mahasa *et al.*, 2017)
c	virus clearance rate	$2.5 * 10^{-2}$	(Friedman *et al.*, 2006) (Paiva *et al.*, 2009
b	death rate of immune cells	$2 * 10^{-2}$	(Mahasa *et al.*, 2017)
β	Infection rate	$7 * 10^{-10}$	(Mahasa *et al.*, 2017)
d	death rate of uninfected cells	0.001	(Mahasa *et al.*, 2017)
α	virus production rate	$1 * 10^{-4}$	(Malinzi *et al.*, 2017)

Table 4.1: Definition of state variables model parameters

The sensitivity indices of the four parameters that we took more interest in as mentioned earlier are as follows:

parameter	Sensitivity Index
δ	-0.99934
β	-0.00065

Table 4.2: Sensitivity Index of the total size of tumor (at equilibrium) in respect of the model parameters

From the Table (4.2), we can see that a 1% increase in δ, induces a 0.99934% reduction in the tumor size, which is around 1500 times higher than the relative change obtained from increasing β. This is a very interesting result as δ does not even appear in the expression of $\mathcal{R}_0$ so one would think that δ is not as relevant in tumor reduction.

While all this is good and well, the model does not account for anti-viral immune response. In the next section, we investigate the effect of anti-viral immune response on the virotherapy.

4.3 Basic model with immune response

We extended a model from the previous section by including a Cytolytic T- Lymphocytes (CTLs) immune response to viral infection, as discussed in the literature review. The

resulting model reads as follows:

$$\begin{cases} \frac{d}{dt}S(t) = \lambda - \beta SV - dS \\ \frac{d}{dt}I(t) = \beta SV - \delta I - \gamma IZ \\ \frac{d}{dt}V(t) = N\delta I - cV \\ \frac{d}{dt}Z(t) = \alpha IZ - bZ \end{cases} \tag{4.3.1}$$

where

- Z represents the population of virus-specific immune cells
- γIZ represents the death rate of productively infected cells due to the response of the immune
- αIZ represents the rate at which immune cells are produced
- b represents immune cells death rate

4.3.1 Equilibrium points and Stability

Once we set the right hand side of (4.3.1) to zero, we deduce the equilibrium points:

$$\begin{cases} \lambda - \beta SV - dS = 0 \\ \beta SV - \delta I - \gamma IZ = 0 \\ N\delta I - cV = 0 \\ Z\left(\alpha I - b\right) = 0 \end{cases} \tag{4.3.2}$$

From $(4.3.2)_4$, we get that

$$Z = 0, \text{ or, } I = \frac{b}{\alpha}.$$

1. If $Z = 0$, then, by following the same steps as for the model without immune response studied in the previous section, we obtain a virus-free equilibrium point

   $$VFE = (S_0, 0, 0, 0)$$

   and a virus-infected equilibrium (VIE)

   $$VIE = \left(\frac{S_0}{\mathcal{R}_0}, \frac{cd}{N\beta\delta}\left(\mathcal{R}_0 - 1\right), \frac{d}{\beta}\left(\mathcal{R}_0 - 1\right), 0\right)$$

Note that VIE is biologically feasible if and only if $\mathcal{R}_0 > 1$.

2. If $Z \neq 0$, then by equation $(4.3.2)_4$ we obtain that

$$I = \frac{b}{\alpha}$$

and consequently, from $(4.3.2)_3$, we have

$$V = \frac{N\delta b}{c\alpha}.$$

Substituting these two expressions back into $(4.3.2)_1$ and $(4.3.2)_2$, we obtain

$$\begin{cases} \lambda - \frac{\beta N\delta b}{c\alpha} S - dS = 0 \\ Z = \frac{\delta}{\gamma}\left(\frac{N\beta}{c} S - 1\right). \end{cases} \tag{4.3.3}$$

$(5.3.5)_1$ implies that

$$S = \frac{\lambda}{d + \frac{\beta N\delta b}{c\alpha}} = \frac{S_0}{1 + q\frac{b}{\alpha}}$$

where

$$S_0 = \frac{\lambda}{d} \text{ and } q = \frac{\beta N\delta}{dc}$$

Substituting the expression of R_{τ_1} and S into $(5.3.5)_2$ we obtain

$$\begin{aligned} Z &= \frac{\delta}{\gamma}\left(\frac{N\beta}{c}\frac{S_0}{1 + q\frac{b}{\alpha}} - 1\right) \\ &= \frac{\delta}{\gamma}\left(\frac{\mathcal{R}_0}{1 + q\frac{b}{\alpha}} - 1\right) \\ &= \frac{\delta}{\gamma\left(1 + q\frac{b}{\alpha}\right)}\left(\mathcal{R}_0 - \left(1 + q\frac{b}{\alpha}\right)\right). \end{aligned}$$

This gives us the interior equilibrium point

$$\bar{E} = \left(\frac{S_0}{1 + q\frac{b}{\alpha}}, \frac{b}{\alpha}, \frac{N\delta b}{c\alpha}, \frac{\delta}{\gamma\left(1 + q\frac{b}{\alpha}\right)}\left(\mathcal{R}_0 - \left(1 + q\frac{b}{\alpha}\right)\right)\right)$$

For the interior equilibrium point to be biologically feasible, we must have the following condition

$$\mathcal{R}_0 > 1 + q\frac{b}{\alpha}.$$

Theorem 4.3.1. *1. If $\mathcal{R}_0 < 1$, the virus-free equilibrium point*

$$VFE = (S_0, 0, 0, 0)$$

is the only non-negative equilibrium point of (4.2.1) and it is locally asymptotically stable.

2. *If $1 < \mathcal{R}_0 < 1 + q\frac{b}{\alpha}$, VFE becomes unstable and the virus infected equilibrium point*

$$VIE = \left(\frac{S_0}{\mathcal{R}_0}, \frac{cd}{N\beta\delta}\left(\mathcal{R}_0 - 1\right), \frac{d}{\beta}\left(\mathcal{R}_0 - 1\right), 0 \right)$$

exists and is locally asymptotically stable.

3. *$\mathcal{R}_0 > 1 + q\frac{b}{\alpha}$, VFE and VIE are unstable and an interior equilibrium point*

$$\bar{E} = \left(\frac{S_0}{1 + q\frac{b}{\alpha}}, \frac{b}{\alpha}, \frac{N\delta b}{c\alpha}, \frac{\delta}{\gamma\left(1 + q\frac{b}{\alpha}\right)}\left(\mathcal{R}_0 - \left(1 + q\frac{b}{\alpha}\right)\right) \right), \; q := \frac{N\beta\delta}{cd}$$

exists and is locally asymptotically stable.

Proof. The existence of the equilibrium points has already been discussed in the beginning of this section. The stability properties of an equilibrium point $E = (S, I, V, Z)$ is calculated via eigen values of the Jacobian. We have

$$J_E = \begin{bmatrix} -d - \beta V & 0 & -\beta S & 0 \\ \beta V & -\delta - \gamma Z & \beta S & -\gamma I \\ 0 & N\delta & -c & 0 \\ 0 & \alpha Z & 0 & \alpha I - b \end{bmatrix}$$

- At VFE, we have

$$J_{VFE} = \begin{bmatrix} -d & 0 & -\frac{\beta\lambda}{d} & 0 \\ 0 & -\delta & \frac{\beta\lambda}{d} & 0 \\ 0 & N\delta & -c & 0 \\ 0 & 0 & 0 & -b \end{bmatrix}$$

From roots of characteristic polynomial we acquire eigenvalues

$$(X + b)(X + d)\left(X^2 + X(\delta + c) + c\delta(1 - \mathcal{R}_0)\right) = 0.$$

Hence VFE is locally asymptotically stable if and only if $\mathcal{R}_0 < 1$.

- At VIE, we have

$$VIE = \left(\frac{S_0}{\mathcal{R}_0}, \frac{cd}{N\beta\delta}\left(\mathcal{R}_0 - 1\right), \frac{d}{\beta}\left(\mathcal{R}_0 - 1\right), 0 \right)$$

$$J_{VIE} = \begin{bmatrix} -d - \beta V & 0 & -\beta S & 0 \\ \beta V & -\delta & \beta S & -\gamma I \\ 0 & N\delta & -c & 0 \\ 0 & 0 & 0 & \alpha I - b \end{bmatrix}$$

with characteristic polynomial

$$\xi = \left(X - \left(\alpha I - b\right)\right)\chi,$$

where χ is the characteristic polynomial calculated in the previous section given by

$$\chi = X^3 + A_2X^2 + A_1X + A_0$$

with

$$\begin{aligned} A_0 &= \delta\left(cd + Vc\beta - NSd\beta\right) \\ A_1 &= \left(\delta\left(d + V\beta\right) + c\left(d + \delta + V\beta\right) - NS\beta\delta\right) \\ A_2 &= \left(c + d + \delta + V\beta\right). \end{aligned}$$

We have established in the previous section that if $\mathcal{R}_0 > 1$, then all roots of the characteristic polynomial χ have negative real parts. Hence VIE is locally asymptotically stable if $\alpha I - b < 0$. This is true if and only if $\frac{cd}{N\beta\delta}\left(\mathcal{R}_0 - 1\right) < \frac{b}{\alpha}$, that is

$$\mathcal{R}_0 < q\frac{b}{\alpha} := 1 + \frac{bN\beta\delta}{\alpha cd}.$$

- At $\bar{E} = \left(\frac{S_0}{1+q\frac{b}{\alpha}}, \frac{b}{\alpha}, \frac{N\delta b}{c\alpha}, \frac{\delta}{\gamma\left(1+q\frac{b}{\alpha}\right)}\left(\mathcal{R}_0 - \left(1 + q\frac{b}{\alpha}\right)\right)\right)$

$$\begin{aligned} J_{\bar{E}} &= \begin{bmatrix} -d - \beta\frac{N\delta b}{\alpha c} & 0 & -\beta S & 0 \\ \beta\frac{N\delta b}{\alpha c} & -\delta - \gamma Z & \beta S & -\gamma\frac{b}{\alpha} \\ 0 & N\delta & -c & 0 \\ 0 & \alpha Z & 0 & 0 \end{bmatrix} \\ &= \begin{bmatrix} -d - dQ & 0 & -\beta S & 0 \\ dQ & -\delta - \gamma Z & \beta S & -\gamma\frac{b}{\alpha} \\ 0 & N\delta & -c & 0 \\ 0 & \alpha Z & 0 & 0 \end{bmatrix} \end{aligned}$$

Using Maple, we calculate the characteristic polynomial of this equation, we find the following fourth order polynomial

$$\zeta = B_0X^4 + B_1X^3 + B_2X^2 + B_3X + B_{4,}$$

where

$$\begin{aligned}
B_0 &= 1,\\
B_1 &= (c + d + \delta + Z\gamma + Qd,)\\
B_2 &= d\left(1 + q\tfrac{b}{\alpha}\right)(\delta + Z\gamma) + cd\left(1 + q\tfrac{b}{\alpha}\right) + c(\delta + Z\gamma) + Zb\gamma - N\beta\delta S,\\
B_3 &= cd\delta\left(1 + q\tfrac{b}{\alpha}\right) + Z\gamma\left(bc + (bd + cd)\left(1 + q\tfrac{b}{\alpha}\right)\right) - Nd\beta\delta S,\\
B_4 &= Zbcd\gamma\left(q\tfrac{b}{\alpha} + 1\right).
\end{aligned}$$

The principal diagonal minors of the Hurwitz matrix associated with the polynomial ζ are given by:

$$\begin{aligned}
&B_i, i = 0, ..., 4,\\
&B_1B_2 - B_0B_3,\\
&B_1B_2B_3 - B_1^2B_4 - B_0B_3^2.
\end{aligned}$$

One can show that when $\mathcal{R}_0 > 1 + q\frac{b}{\alpha}$ the above principal diagonal minors are positive which by Routh-Hurwitz criterion (DeJesus and Kaufman, 1987) imply that all roots of ζ have negative real parts and therefore $\bar{E}$ is locally asymptotically stable.

□

We note here that when the antiviral immune response exists, the condition $\mathcal{R}_0 > 1$ is no longer sufficient for the viral infection to persist. In fact, the threshold for persistence of the virus is higher than 1, we must have

$$\mathcal{R}_0 > 1 + q\frac{b}{\alpha}.$$

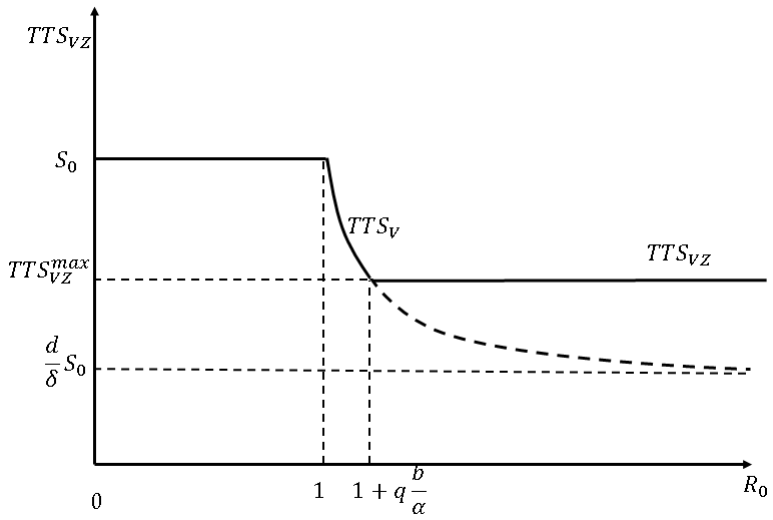


Figure 4.3: Bifurication Diagram 2

This bifurcation diagram 4.3 shows that without virotherapy, the total tumor size (TTS) stabilizes at S_0. The introduction of a "weak" virotherapy $(R_0 < 1)$ is incapable of reducing the TTS. However, when using an oncolytic virus with an "intermediate" reproductive number $(1 < R_0 < 1 + q\frac{b}{\alpha})$, the TTS decreases with higher values of R_0) to reach a minimum value of $\frac{S_O}{1+q\frac{b}{\alpha}}((1-\frac{d}{\delta})+\frac{d}{\delta}) > S_0\frac{d}{\delta}$ at $R_0 = 1 + q\frac{b}{\alpha}$. Beyond this value of R_0, the TTS remains constant. This suggests that there is no benefit of using oncolytic viruses with a "high" reproductive number $(R_0 > 1 + q\frac{b}{\alpha})$ as this will not lead to any further reduction in the TTS and may only cause some undesirable side-effects.

4.4 Review of the Bazjer model

We now look into an existing model analysed by Bazjer et al. in (Bajzer *et al.*, 2008) who studied the use of a measles virus for oncolytic virotherapy. The model proposed consists of three differential equations representing two tumor populations which are uninfected and infected respectively and the virus population. Upon contact of the tumor with the measles virus, cells clump together forming *synctia* which is a multi-nucleated cell (Zsak *et al.*, 1992), that eventually dies. They also can reproduce new viruses meaning more tumor cells get infected and the cycle continues throughout treatment.

The resulting model reads as follows:

$$\frac{dy}{dy} = ry[1 - (y + x)^{\epsilon} / K^{\epsilon}] - kyv - \rho xy \tag{4.4.1}$$

$$\frac{dx}{dx} = kyv - \delta x \tag{4.4.2}$$

$$\frac{dv}{dt} = \alpha x - \omega v - kyv \tag{4.4.3}$$

- y is the population of uninfected cells where r depicts rate of growth; K the carrying capacity and parameter $\rho > 0$ being the constant rate which describes fusion of cells.
- x is the combined population of both infected cells and synctia dying at the rate $\delta > 0$.
- The virus population is denoted by v with α being the constant rate at which the viruses are produced per day per cell; ω is the constant rate at which viruses die and k is the rate of infection per day for every 10^6 cells or virons.

This model assumed that a tumor would be removed if the total tumor population is one cell but this is not feasible biologically.

Parameter estimation and data fitting was done as well as the stability analysis. Lastly, numerical simulations helped to determine conditions which favoured successful virotherapy and validate the model.

We extend this model by introducing an immune response and also extend their schematic diagram to cater for the extension. Further on we discuss a simple virotherapy model which again, includes tumor population as well as virus. The model is not novel and has been adopted from other standard HIV and population dynamics models (Heuveline, 2003; Jenner *et al.*, 2018; Phan and Tian, 2017). We calculate its equilibrium points, reproductive number as well as the sensitivity index to get the most important parameter.

The extended model would be characterized as:

$$\frac{dy}{dt} = ry[1-(y+x)^{\epsilon}/K^{\epsilon}] - kyv - \rho xy \tag{4.4.4}$$

$$\frac{dx}{dt} = kyv - \delta x \tag{4.4.5}$$

$$\frac{dv}{dt} = \alpha x - \omega v - kyv \tag{4.4.6}$$

$$\frac{dz}{dt} = cxz - bz \tag{4.4.7}$$

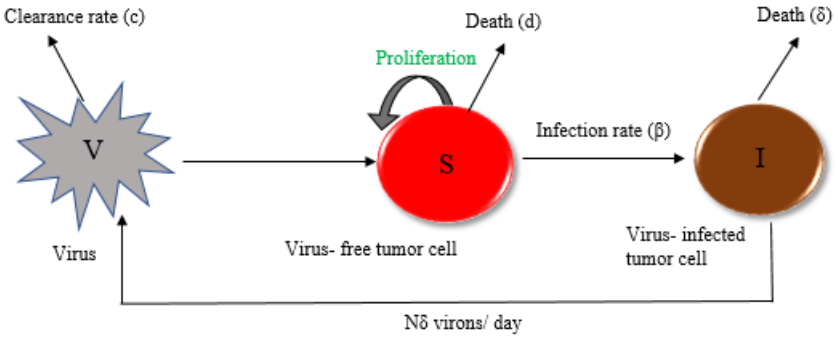


Figure 4.4: Basic Viral Infection Model with Proliferation of Uninfected Cells

In this extended model, the new population z is that of the immune cells where the parameter c is the proliferation rate due to the infected tumor cells x, and b is the death rate.

We can schematically model this as seen below where the solid arrows depict the population growth/influx and the dotted lines are indicative of the dependency of corresponding rates on the population of uninfected cells x.

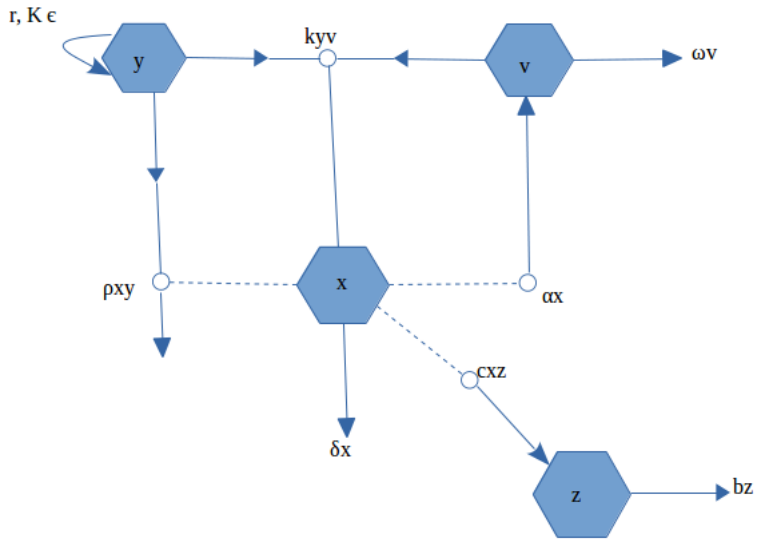


Figure 4.5: Schematic representation of tumor-cell-immune interaction (Bajzer *et al.*, 2008)

4.5 Summary

We considered and analysed the first two models mathematically taking into account a constant tumor growth rate λ, which was extended by (Bajzer *et al.*, 2008) to a logistic proliferation rate. (The mathematical analysis of the latter was not carried out as it will be done for a more general case). All these models focus on the oncolytic potency of the virus $\mathcal{R}_0$ and the strength of the immune response $\frac{b}{a}$, but don't account either for the speed of viral replication and/or the speed at which the immune system responds. In the next chapter, we introduce a model with a non-constant proliferation rate that includes two delays to account for the speed of the viral replication and immune response.

Chapter 5

Delay Model

5.0.1 Introduction

In the previous chapter we considered an ODE based model of virotherapy. However, for some tumors, oncolytic viruses can only be administered intravenously as direct viral injections can be harmful. However, this method of introducing the viruses into the host's system, poses a big challenge with virus delivery as the virus becomes more prone to the immune response (Kirn *et al.*, 2001). The success of such treatment depends on, among other factors, how quick the viral replication is and how slow is the antiviral immune response is.

Delays involved are:

1. **Immune response delay:** modelled as time delay for immune system to develop suitable response once it recognizes virus-infected cells (Prestwich *et al.*, 2008; Timalsina *et al.*, 2017) and
2. **Intracellular delay:** modelled as the time between attachment of a virus to a cell and the production of new viruses. (Tian *et al.*, 2016; Xu, 2011).

We are interested in the effects that these delays may have on the overall effect of oncolytic virotherapy. Faster viral replication often leads to higher oncolytic effects and hence tumor reduction, while faster antiviral immune responses hinder viral replication leading to tumor growth. We aim in this chapter to find a trade-off between these two delays that optimizes oncolytic virotherapy. We note here that the modelling of

the simultaneous effect of two delays in oncolytic virotherapy has not been addressed previously.

5.1 Basic model with logistic growth

The model that we consider in this section is an extension of the basic model without immune response considered in the previous chapter by considering a logistic growth for the tumor population. The resulting model reads as follows:

$$\begin{cases} \frac{dS}{dt} = rS(1 - k(S + I)) - \beta SV - dS \\ \frac{dI}{dt} = \beta SV - \delta I \\ \frac{dV}{dt} = pI - cV \end{cases}$$

where

- $S(t)$: Uninfected tumor cells
- $I(t)$: Productively infected tumor cells (meaning that they are specifically those that are able to produce viruses)
- $V(t)$: Population of oncolytic viruses
- r: Logistic proliferation rate of tumor cells that aren't infected
- $\frac{1}{k}$: Total volume of uninfected tumor cells
- βSV: Infection rate of the uninfected tumor cells
- d: Per capita death rate of uninfected tumor cells
- δ: Per capita death rate (due to lysis) of productively infected cells
- $pI(t)$: Production rate of the oncolytic viruses by productively infected cells
- c: Clearance rate of oncolytic viruses

As in the prior chapter, we'll analyse the model's reproductive number, equilibria and their stability properties.

5.1.1 Reproductive number ($\mathcal{R}_0$)

Before applying the next generation method to calculate $\mathcal{R}_0$, we note that due to the logistic proliferation rate, the model exhibits two virus-free equilibrium points as established in the following proposition. Therefore, it is key to choose the right disease-free equilibrium point in our implementation of the next generation method. In fact, when there is no virus, the model simplifies to the following scalar equation

$$\frac{dS}{dt} = rS(1 - kS) - dS \tag{5.1.1}$$

which has the following stability properties:

Proposition 5.1.1. *1. If $r < d$ then model (5.1.1) has only one non-negative equilibrium point $\Theta = 0$. Moreover, Θ is locally asymptotically stable.*

2. If $r > d$, then Θ is unstable and (5.1.1) has an additional non-negative equilibrium point, $S_0 = \frac{r-d}{rk}$, that is locally asymptotically stable.

Proof. The existence of the (virus-free) equilibrium points is obvious, their stability can be determined by the sign of

$$J_S := \frac{d}{dS}\left(rS(1 - kS) - dS\right) = r - d - 2Skr.$$

- At $S = 0$, we obtain $J_0 = r - d$. Hence, Θ is locally asymptotically stable if $r < d$ and unstable if $r > d$.
- At $S_0 = \frac{r-d}{rk}$, we obtain $J_{S_0} = d - r$. Hence, S_0 is locally asymptotically stable if $r > d$ and unstable if $r < d$.

□

Remark 5.1.2. *We note that the equation (5.1.1) can be solved explicitly, making the (local) stability results global.*

Based on the above proposition, we see that when $r < d$, there is no tumor cells and therefore we do not need to perform any virotherapy. We therefore focus for the remainder of this chapter on the case $r > d$, which makes the model stabilize at the (virus-free)

equilibrium point $S_0 = \frac{r-d}{rk}$. It is at this equilibrium that we deduce the basic reproductive number of (5.2.1).

Commencing by sorting the equations of model (5.1) so that the first equations are for the infected classes, we obtain

$$\begin{cases} \dfrac{dI}{dt} = \beta SV - \delta I \\ \dfrac{dV}{dt} = pI - cV \\ \dfrac{dS}{dt} = rS\left(1 - k\left(S + I\right)\right) - \beta SV - dS \end{cases}$$

The disease free equilibrium of this model is given by $x_0 = (0, 0, S_0)$, the rate of new infections is $F = \begin{bmatrix} \beta SV \\ 0 \end{bmatrix}$ and that of other transfers is given by $W = \begin{bmatrix} \delta I \\ -N\delta I + cV \end{bmatrix}$. The next generation matrix is given by

$$\begin{aligned} DF(x_0)\left[DW(x_0)\right]^{-1} &= \begin{bmatrix} 0 & \beta S_0 \\ 0 & 0 \end{bmatrix} \begin{bmatrix} \delta & 0 \\ -p & c \end{bmatrix}^{-1} \\ &= \begin{bmatrix} \frac{p}{\delta c}\beta S_0 & \frac{1}{c}\beta S_0 \\ 0 & 0 \end{bmatrix}. \end{aligned}$$

The basic reproductive number is then

$$\mathcal{R}_0 = \rho\left(DF(x_0)\left[DW(x_0)\right]^{-1}\right) = \rho\left(\begin{bmatrix} \frac{p}{\delta c}\beta S_0 & \frac{1}{c}\beta S_0 \\ 0 & 0 \end{bmatrix}\right).$$

Finally, we obtain

$$\mathcal{R}_0 = \frac{\beta p}{\delta c} S_0 = \frac{\beta p\left(r - d\right)}{\delta crk}.$$

We note that $R_0 > 0$ because we assume that $r > d$.

5.1.2 Equilibrium points and stability

From positive solutions of the following system, we deduce equilibrium points.

$$\begin{cases} rS\left(1 - k\left(S + I\right)\right) - \beta SV - dS = 0 \\ I\left(\frac{p\beta}{\delta c}S - 1\right) = 0 \\ V = \frac{p}{c}I \end{cases} \tag{5.1.2}$$

From $(5.1.2)_2$, we have $I = 0$ or $S = \frac{\delta c}{p\beta}$.

1. If $I = 0$, then by $(5.1.2)_3$ we have $V = 0$ which, together with $(5.1.2)_1$, lead to $S = 0$ or $S = \frac{r-d}{rk}$.
   In the first case, we obtain the trivial equilibrium point

$$\Theta = (0, 0, 0)\,.$$

   In the second case, we obtain the virus-free equilibrium point

$$VFE = \left(\frac{r-d}{rk}, 0, 0\right)$$

2. If $S = \frac{\delta c}{p\beta}$, then by substituting this expression along with $(5.1.2)_3$ into $(5.1.2)_1$ and solving for I, we obtain

$$I = \frac{\delta c^2 rk}{p\beta\,(crk + p\beta)}\left(\frac{(r-d)p\beta}{\delta crk} - 1\right).$$

   Then

$$I = \frac{\delta c^2 rk}{p\beta(crk + p\beta)}\,(R_0 - 1) \tag{5.1.3}$$

   or, equivalently,

$$I = S_0 B\left(1 - \frac{1}{\mathcal{R}_0}\right), \text{ where } B = \frac{crk}{crk + \beta p.} \tag{5.1.4}$$

   By $(5.1.2)_3$, we have

$$V = \frac{p}{c}I = \frac{\delta crk}{\beta(crk + p\beta)}\,(\mathcal{R}_0 - 1)\,.$$

   Hence we obtain the virus-infected equilibrium

$$VIE = \left(\frac{\delta c}{p\beta}, \frac{\delta c^2 rk}{p\beta(crk + p\beta)}\,(\mathcal{R}_0 - 1)\,, \frac{\delta crk}{\beta(crk + p\beta)}\,(\mathcal{R}_0 - 1)\right).$$

   It's of great significance to note that VIE is biologically feasible only when $\mathcal{R}_0 > 1$. We have the following proposition:

Proposition 5.1.3. *1. If $r < d$, then model (5.1) has only one non-negative equilibrium point*

$$\Theta = (0, 0, 0)$$

which is locally asymptotically stable.

2. *If $r > d$, then Θ becomes unstable and the virus-free equilibrium point*

$$VFE = \left(\frac{r-d}{rk}, 0, 0\right)$$

exists. Moreover,

a) If $\mathcal{R}_0 < 1$, then VFE is locally asymptotically stable.

b) If $\mathcal{R}_0 > 1$, then VFE becomes unstable and

$$VIE = \left(\frac{\delta c}{p\beta}, \frac{\delta c^2 rk}{p\beta(crk + p\beta)}\left(\mathcal{R}_0 - 1\right), \frac{\delta crk}{\beta(crk + p\beta)}\left(\mathcal{R}_0 - 1\right)\right).$$

is non-negative and is locally asymptotically stable.

That is the model exhibits a transcritical bifurcation at $\mathcal{R}_0 = 1$.

Proof. The existence of these equilibria being already established, we restrict the proof to the stability results which can be deduced from the eigenvalues of the Jacobian matrix:

$$J_E = \begin{pmatrix} r - d - 2rkS - rkI - \beta V & -rkS & -\beta S \\ \beta V & -\delta & \beta S \\ 0 & p & -c \end{pmatrix}.$$

1. At the trivial equilibrium point Θ, we have

$$J_\Theta = \begin{pmatrix} r-d & 0 & 0 \\ 0 & -\delta & 0 \\ 0 & p & -c \end{pmatrix}$$

whose eigenvalues include $r - d, -\delta$ as well as $-c$. Hence Θ is locally asymptotically stable.

2. At the virus-free equilibrium point VFE, we have

$$J_{VFE} = \begin{pmatrix} d-r & d-r & -\beta\frac{r-d}{rk} \\ 0 & -\delta & \beta\frac{r-d}{rk} \\ 0 & p & -c \end{pmatrix}$$

which has the following characteristic polynomial:

$$\left(X - (r-d)\right)\left(X^2 + (\delta + c)\,X + c\delta\left(1 - \mathcal{R}_0\right)\right)$$

Hence by the Routh-Hurwitz criterion, VFE that's locally asymptotically stable when $r < d$ and $\mathcal{R}_0 < 1$ and is unstable if $r > d$ or $\mathcal{R}_0 > 1$.

3. At the virus-infected equilibrium point VIE, we have

$$J_{VIE} = \begin{pmatrix} r - d - 2rkS - rkI - \beta V & -rkS & -\beta S \\ \beta V & -\delta & \beta S \\ 0 & p & -c \end{pmatrix}$$

Using $(5.1.2)_1$ and the fact that $S \neq 0$, we obtain $r - d - rkS - rkI - \beta V = 0$. Hence the first entry of J_{VIE} reduces to

$$r - d - 2rkS - rkI - \beta V = -rkS.$$

Thus the Jacobian matrix reduces to

$$J_{VIE} = \begin{pmatrix} -rkS & -rkS & -\beta S \\ \beta V & -\delta & \beta S \\ 0 & p & -c \end{pmatrix}$$

which has the following characteristic polynomial:

$$\psi = X^3 + A_2X^2 + A_1X + A_0$$

where

$$\begin{aligned} A_2 &= c + \delta + Skr > 0 \\ A_1 &= c\delta - Sp\beta + cSkr + Skr\delta + SVkr\beta \\ A_0 &= S\left(\left(p\beta + ckr\right)\beta V + ckr\delta - kpr\beta S\right) \end{aligned}$$

Since $S = \frac{\delta c}{p\beta}$, then

$$\begin{aligned} A_1 &= Skr\left(c + \delta + \beta V\right) \\ A_0 &= \left(p\beta + ckr\right)\beta SV \end{aligned}$$

Hence, if $\mathcal{R}_0 > 1$, then $V > 0$ implying that $A_0 > 0$ and $A_1 > 0$. Moreover, we have $A_1A_2 > A_0$, then by the Routh-Hurwitz criterion, VIE is locally asymptotically stable if $r < d$ and is unstable if $r > d$.

□

As done in the previous chapter for the model with constant tumor growth rate, we investigate next how, in the case of logistic tumor growth rate, virotherapy reduces the Total Tumor Size at equilibrium (TTS) which is given by

$$TTS = \frac{\delta c}{p\beta} + \frac{\delta c^2 rk}{p\beta(crk + p\beta)}\left(\mathcal{R}_0 - 1\right).$$

Proposition 5.1.4. *If $\mathcal{R}_0 > 1$, then $TTS < S_0$.*

Proof. Since $\mathcal{R}_0 = \frac{\beta p(r-d)}{\delta crk}$, then

$$TTS = \frac{c\,(\delta + r - d)}{p\beta + ckr}. \tag{5.1.5}$$

Hence,

$$TTS - S_0 = \frac{c\,(\delta + r - d)}{p\beta + ckr} - \frac{r-d}{rk} = \frac{ckr\delta - p\beta\,(r-d)}{kr\,(p\beta + ckr)}.$$

Since $\mathcal{R}_0 > 1$, then $ckr\delta - p\beta\,(r-d) < 0$ implying that $TTS < S_0$. □

Remark 5.1.5. *Concerning the behaviour of TTS with respect to the virus parameters we deduce from (5.1.5) that TTS is decreasing with respect to p and β, and increasing with respect to c and δ.*

For illustration purposes, we depict, in the next bifurcation diagram, the behaviour of TTS with respect to β and δ. We first note that if other parameters are fixed,

$$\begin{cases} \mathcal{R}_0 > 1 & \text{if and only if} \quad \beta > \beta_c := \frac{\delta crk}{p(r-d)}, \\ \mathcal{R}_0 > 1 & \text{if and only if} \quad \delta < \delta_c := \frac{\beta p(r-d)}{crk}. \end{cases}$$

We also note that

$$\begin{cases} TTS = S_0 & \text{when} \quad \beta = \beta_c := \frac{\delta crk}{p(r-d)}, \\ TTS \to 0 & \text{when} \quad \beta \to \infty. \end{cases}$$

and

$$\begin{cases} TTS = S_0 & \text{when} \quad \delta = \delta_c := \frac{\beta p(r-d)}{crk}, \\ TTS = TTS_0 := \frac{c(r-d)}{p\beta + ckr} & \text{when} \quad \delta = 0. \end{cases}$$

This leads to the following bifurcation diagrams

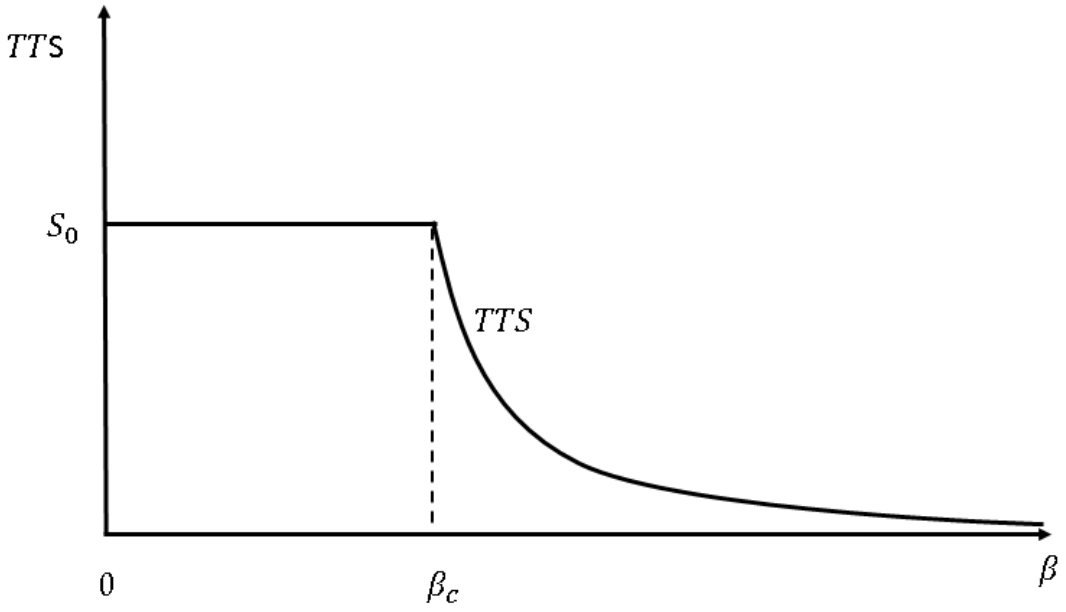


Figure 5.1: Bifurcation diagram of TTS with respect to β

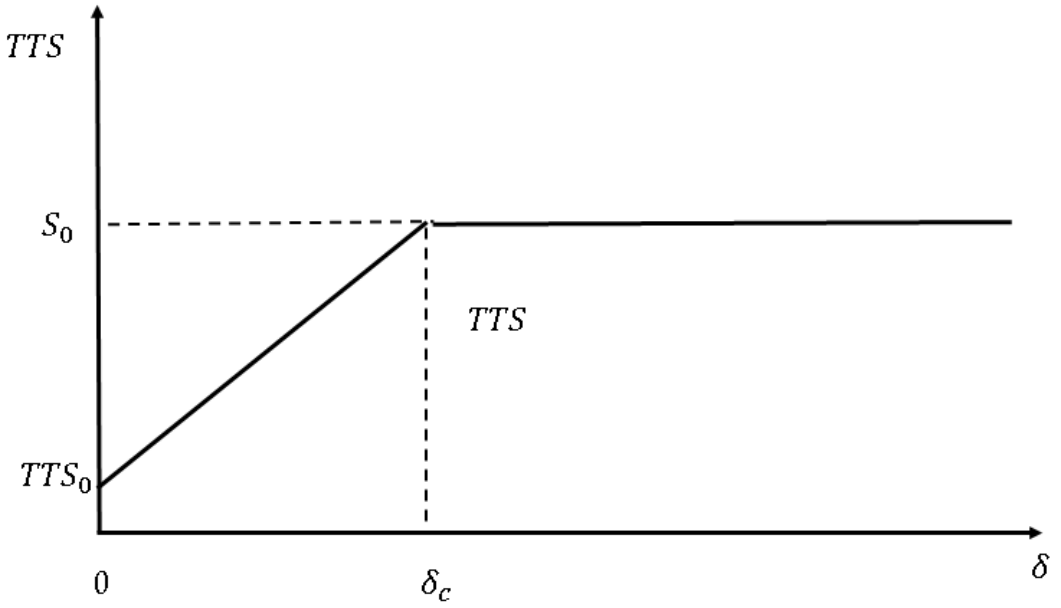


Figure 5.2: Bifurcation diagram of TTS with respect to δ

5.2 Adding an intracellular delay

In this section, we extend model (5.1) by adding an intracellular delay to account for the time required for infected cells to start producing viruses. The resulting model reads as follows:

$$\begin{cases} \dfrac{dS}{dt} = rS(1-k(S+I)) - \beta SV - dS, \\ \dfrac{dI}{dt} = \beta e^{-d\tau_1} S\left(t-\tau_1\right) V\left(t-\tau_1\right) - \delta I, \\ \dfrac{dV}{dt} = pI - cV, \end{cases} \tag{5.2.1}$$

where

- τ_1: Time delay since infection for the infected cells to become productively infected provided they survive this period
- $e^{-d\tau_1}$: Probability of survival of infected cells.

5.2.1 Reproductive number (R_0)

It is important to note that the next generation method used to calculate $\mathcal{R}_0$ was developed only for ODE-based models. Therefore, in this section, we will calculate $\mathcal{R}_0$ by means of the "intuition" method as described below:

Assume that at time $t = 0$, the model is at the disease-free equilibrium $VFE = (S_0, 0, 0, 0)$ where $S_0 = \frac{r-d}{kd}$

a. One virus leads to $e^{-d\tau_1}\beta S_0$ new infections per unit time, causing $\frac{e^{-d\tau_1}\beta S_0}{c}$ new infections during its entire lifetime.

b. Each infected cell will produce p new viruses per unit time, leading to $\frac{p}{\delta}$ new viruses during its entire lifetime.

c. Hence each virus will lead to the production of $\frac{e^{-d\tau_1} p\beta S_0}{\delta c}$ new viruses during its entire lifetime.

Therefore, the basic reproduction number is

$$\mathcal{R}_{\tau_1} = \frac{(r-d)\beta p e^{-d\tau_1}}{rk\delta c}.$$

We note that

$$R_{\tau_1} = R_0 e^{-d\tau_1},$$

where $\mathcal{R}_0$ is the basic reproductive number of the model without delay.

5.2.2 Equilibrium points and stability

The equilibrium points are given by the positive solutions of the following system:

$$\begin{cases} rS\left(1-k\left(S+I\right)\right)-\beta\frac{p}{c}SI-dS=0 \\ I\left(\frac{p\beta e^{-d\tau_1}}{\delta c}S-1\right)=0 \\ V=\frac{p}{c}I \end{cases} \tag{5.2.2}$$

From $(5.2.2)_2$, we have $I=0$ or $S=\frac{\delta c}{p\beta e^{-d\tau_1}}$.

1. If $I=0$, then by $(5.2.2)_3$ we have $V=0$ which, together with $(5.2.2)_1$, lead to $S=0$ or $S=\frac{r-d}{rk}$.
   In the first case, we obtain the trivial equilibrium point

   $$\Theta=\left(0,0,0\right).$$

   In the second case, we obtain the virus-free equilibrium point

   $$VFE=\left(\frac{r-d}{rk},0,0\right).$$

2. If $S=\dfrac{\delta c}{p\beta e^{-d\tau_1}}$, then by solving $(5.2.2)_1$ for I and substituting the expression S, we obtain

   $$\begin{aligned} I &= \frac{\left(c\left(r-d\right)-Sckr\right)}{p\beta+ckr} \\ &= \frac{c\left(p\beta\left(r-d\right)-ckr\delta e^{d\tau_1}\right)}{p\beta\left(p\beta+ckr\right)} \\ &= \frac{c^2kr\delta e^{d\tau_1}\left(R_{\tau_1}-1\right)}{p\beta\left(p\beta+ckr\right)}. \end{aligned}$$

   By $(5.2.2)_3$, we have

   $$V=\frac{p}{c}I=\frac{ckr\delta e^{d\tau_1}\left(\mathcal{R}_{\tau_1}-1\right)}{\beta\left(p\beta+ckr\right)}.$$

Hence we obtain the virus-infected equilibrium

$$VIE = \left(\frac{\delta c}{p\beta e^{-d\tau_1}}, \frac{c^2 kr\delta e^{d\tau_1}\left(\mathcal{R}_{\tau_1} - 1\right)}{p\beta\left(p\beta + ckr\right)}, \frac{ckr\delta e^{d\tau_1}\left(\mathcal{R}_{\tau_1} - 1\right)}{\beta\left(p\beta + ckr\right)} \right).$$

It is important to note that VIE is biologically feasible only when the reproductive number is greater than one. We have the following proposition:

Proposition 5.2.1. *1. If $r < d$, then model (5.2.1) has only one non-negative equilibrium point $\Theta = (0,0,0)$ which is locally asymptotically stable.*

2. If $r > d$, then Θ becomes unstable and the virus-free equilibrium point $VFE = \left(\frac{r-d}{rk}, 0, 0\right)$ is biologically feasible.
Moreover, VFE is locally asymptotically stable if $\mathcal{R}_{\tau_1} < 1$ and is unstable if $\mathcal{R}_{\tau_1} > 1$.

Proof. The existence of these equilibria being already established, we restrict the proof to the stability results which can be deduced from the roots of the characteristic equation

$$\chi_E = \det \begin{pmatrix} r - d - 2rkS - krI - \beta V - \lambda & -rkS & -\beta S \\ \beta e^{-d\tau_1} e^{-\lambda\tau_1} V & -\delta - \lambda & \beta e^{-d\tau_1} e^{-\lambda\tau_1} S \\ 0 & p & -c - \lambda \end{pmatrix}$$

1. At the trivial equilibrium point Θ, we have

$$\begin{aligned} \chi_\Theta &= \det \begin{pmatrix} r - d - \lambda & 0 & 0 \\ 0 & -\delta - \lambda & 0 \\ 0 & p & -c - \lambda \end{pmatrix} \\ &= -\left(\lambda + \delta\right)\left(d - r + \lambda\right)\left(c + \lambda\right) \end{aligned}$$

whose roots are $r - d$, $-\delta$ and $-c$. Hence Θ is locally asymptotically stable if $r < d$.

2. At the virus-free equilibrium point VFE, we have

$$\begin{aligned} \chi_{VFE} &= \det \begin{pmatrix} -\left(r - d\right) - \lambda & -rkS_0 & -\beta S_0 \\ 0 & -\delta - \lambda & \beta e^{-d\tau_1} e^{-\lambda\tau_1} S_0 \\ 0 & p & -c - \lambda \end{pmatrix} \\ &= \left(d - r - \lambda\right)\left(\lambda^2 + \left(\delta + c\right)\lambda + c\delta - p\beta S_0 e^{-d\tau_1} e^{-\lambda\tau_1}\right) \\ &= \left(d - r - \lambda\right)\left(\lambda^2 + \left(\delta + c\right)\lambda + c\delta\left(1 - R_{\tau_1} e^{-\lambda\tau_1}\right)\right). \end{aligned}$$

This is a transcendental equation involving the term $e^{-\lambda\tau_1}$. The investigation of its roots (not presented here) shows that VFE is locally asymptotically stable if and only if $r < d$ and $R_{\tau_1} < 1$ and unstable if $r > d$ or $\mathcal{R}_{\tau_1} > 1$.

□

With regards to the VIE stability,

$$\chi_{VIE} = \det \begin{pmatrix} r - d - 2rkS - krI - \beta V - \lambda & -rkS & -\beta S \\ \beta e^{-d\tau_1} e^{-\lambda\tau_1} V & -\delta - \lambda & \beta e^{-d\tau_1} e^{-\lambda\tau_1} S \\ 0 & p & -c - \lambda \end{pmatrix},$$

using $r - d - rkS - rkI - \beta V = 0$, we obtain

$$\chi_{VIE} = \det \begin{pmatrix} -kS - \lambda & -rkS & -\beta S \\ \beta e^{-d\tau_1} e^{-\lambda\tau_1} V & -\delta - \lambda & \beta e^{-d\tau_1} e^{-\lambda\tau_1} S \\ 0 & p & -c - \lambda \end{pmatrix}.$$

This gives another transendental equation

$$\chi_{VIE} = -\lambda^3 + A_2\lambda^2 + A_1\lambda + A_0$$

where

$$\begin{aligned} A_2 &= -c - \delta - Sk \\ A_1 &= -\left(c\delta + Sk\delta + Sck + (Vkr - p)\,\beta S e^{-d\tau_1} e^{-\lambda\tau_1}\right) \\ A_0 &= -\left(ck\delta S + (V(p\beta + ckr) - kpS)\,\beta S e^{-d\tau_1} e^{-\lambda\tau_1}\right). \end{aligned}$$

The analysis of the roots of these characteristic equations is far off this thesis span. However, the numerical investigation suggests that VIE is unstable if $r > d$ and $\mathcal{R}_{\tau_1} < 1$.

Remark 5.2.2. *Since* $\mathcal{R}_{\tau_1} = \mathcal{R}_0 e^{-d\tau_1}$, *then:*

1. *If* $\mathcal{R}_0 < 1$, *then* $\mathcal{R}_{\tau_1} < 1$ *for all* $\tau_1 > 0$,
2. *If* $\mathcal{R}_0 > 1$, *then* $\mathcal{R}_{\tau_1} > 1$ *if and only if* $\tau_1 < \tau_{1c} := \frac{1}{d}\ln\mathcal{R}_0$.

Thus, using the above remark, we re-write the proposition above in terms of τ_1 to obtain the following result:

Proposition 5.2.3. *1. If $r < d$, then model (5.2.1) has only one equilibrium point $\Theta = (0,0,0)$ which is locally asymptotically stable.*

2. *If $r > d$, then Θ becomes unstable and the virus-free equilibrium point $VFE = \left(\frac{r-d}{rk}, 0, 0\right)$ is biologically feasible.*
   Moreover,

   a) if $\mathcal{R}_0 < 1$, then VFE is locally asymptotically stable for all τ_1.

   b) if $\mathcal{R}_0 > 1$, then the model exhibits a transcritical bifurcation at $\tau_1 = \tau_{1c}$, that is:

   i. *if $\tau_1 > \tau_{1c}$, then VFE is locally asymptotically stable*

   ii. *if $\tau_1 < \tau_{1c}$, then VFE is unstable and VIE is biologically feasible.*

This proposition shows that the condition $\mathcal{R}_0 > 1$ is not enough to sustain a viral infection. In fact, in addition to this condition, the intracellular delay must be small enough. In other words, for viral infection to persist, the virus has to have a high potency ($\mathcal{R}_0 > 1$) and the viral replication must be fast enough (τ_1 small enough).

The tumor size for a given time $\tau_1 < \tau_{1c}$ is given by

$$TTS_{\tau_1} = \frac{\delta c e^{d\tau_1}}{p\beta} + \frac{c^2 kr\delta e^{d\tau_1}\left(\mathcal{R}_{\tau_1} - 1\right)}{p\beta\left(p\beta + ckr\right)}.$$

Proposition 5.2.4. *If $\mathcal{R}_{\tau_1} > 1$, then $TTS_{\tau_1} < S_0$.*

Proof. Since $\mathcal{R}_{\tau_1} = \dfrac{\beta p\left(r-d\right)e^{-d\tau_1}}{\delta crk}$, then

$$TTS_{\tau_1} = \frac{c\left(\delta e^{d\tau_1} + r - d\right)}{p\beta + ckr}. \tag{5.2.3}$$

Hence,

$$\begin{aligned} TTS_{\tau_1} - S_0 &= \frac{c\left(\delta e^{d\tau_1} + r - d\right)}{p\beta + ckr} - \frac{r-d}{rk} \\ &= \frac{ckr\delta e^{d\tau_1} - p\beta\left(r-d\right)}{kr\left(p\beta + ckr\right)}. \end{aligned}$$

Since $\mathcal{R}_{\tau_1} > 1$, then $ckr\delta - \beta p\left(r-d\right)e^{-d\tau_1} < 0$. Hence $TTS_{\tau_1} < S_0$. □

Remark 5.2.5. *We deduce from (5.2.3) that TTS_{τ_1} is increasing with respect to τ_1, moreover, we have*

$$\begin{cases} TTS_{\tau_1} = \dfrac{\delta c \mathcal{R}_0}{p\beta} = S_0 & \text{when} \quad \tau_1 = \tau_{1c} := \frac{1}{d} \ln \mathcal{R}_0, \\ TTS_{\tau_1} = TTS & \text{when} \quad \tau_1 = 0, \end{cases}$$

where TTS is the total tumor size at equilibrium calculated in the model without delay given by

$$TTS = \frac{\delta c}{p\beta} + \frac{\delta c^2 rk}{p\beta(crk + p\beta)} (\mathcal{R}_0 - 1).$$

The variation of TTS with respect to the virus parameters being discussed previously, we present in the diagram below an illustration of the behaviour of TTS_{τ_1} with respect to τ_1.

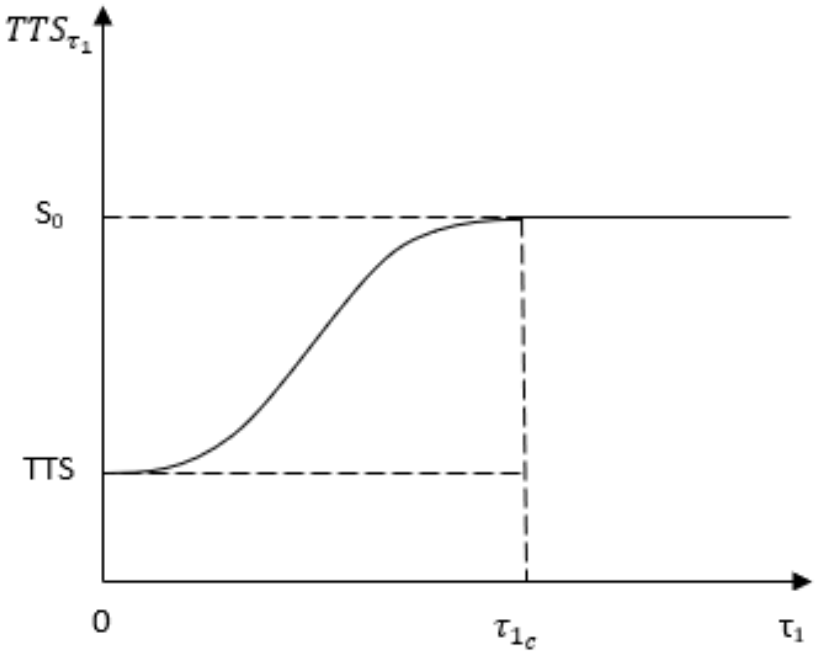


Figure 5.3: Bifurcation diagram of TTS_{τ_1} with respect to τ_1

5.3 Mathematical Model with Immune Response

We extended the model considered in the previous section by (1) accounting for a Cytolytic T- Lymphocites (CTLs) immune response as discussed in the literature review and (2) including an immune reaction delay (Ong *et al.*, 2007) (Yang *et al.*, 2017).

The resulting model reads as follows:

$$\begin{cases} \frac{d}{dt}S(t) = rS(1-k(S+I)) - \beta SV - dS \\ \frac{d}{dt}I(t) = \beta e^{-d\tau_1}(S(t-\tau_1)V(t-\tau_1)) - \delta I - \gamma IZ \\ \frac{d}{dt}V(t) = pI - cV \\ \frac{d}{dt}Z(t) = \alpha IZ - bZ \end{cases}$$

where

- $Z(t)$: Population of virus-specific immune cells
- αIZ: Productively infected cells death rate due to immune response
- b: Death rate of immune cells.

Considering the rate of production rate of immune cells g, one can consider two types of immune responses: $\alpha_1 IZ = \alpha e^{-\delta\tau_2} I(t-\tau_2)Z(t-\tau_2)$ or $\alpha_2(I_t, Z_t) := \alpha e^{-\delta\tau_2} I(t-\tau_2)Z(t)$. For simplicity, we consider an immune response of the form $\alpha IZ := \alpha e^{-\delta\tau_2} I(t-\tau_2)Z(t)$. That is,

$$\begin{cases} \frac{d}{dt}S(t) = rS(1-k(S+I)) - \beta SV - dS \\ \frac{d}{dt}I(t) = e^{-d\tau_1}\beta S\left(t-\tau_1\right)V\left(t-\tau_1\right) - \delta I - \gamma IZ \\ \frac{d}{dt}V(t) = pI - cV \\ \frac{d}{dt}Z(t) = \alpha e^{-\delta\tau_2} I(t-\tau_2)Z(t) - bZ \end{cases} \tag{5.3.1}$$

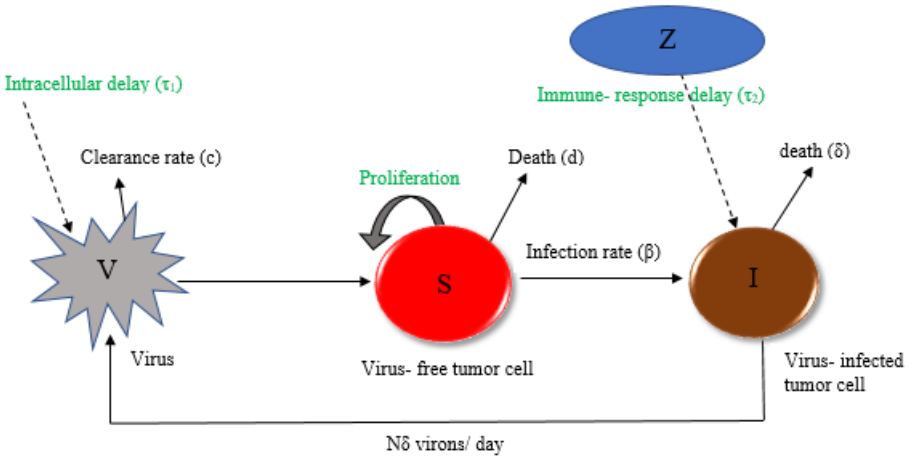


Figure 5.4: Basic viral infection model with time delays

5.3.1 Equilibrium points

We note that, if $r \leq d$ then $S(t)$ tends to zero as t tends to infinity, meaning that there are no tumor cells to study or no therapy to consider. Consequently, in the remainder of this section, we assume that $r > d$.

The equilibrium points of (5.3.1) are achieved by fixing its right hand side to null and solving the resulting equation. This yields :

$$\begin{cases} S\left(r - d - rkS - \left(rk + \frac{p\beta}{c}\right) I\right) = 0 \\ I\left(\frac{p\beta}{c} e^{-d\tau_1} S - \delta - \gamma Z\right) = 0 \\ V = \frac{pI}{c} \\ Z\left(\alpha e^{-\delta\tau_2} I - b\right) = 0 \end{cases} \tag{5.3.2}$$

From $(5.3.2)_4$, we get that

$$Z = 0, \text{ or } I = \frac{be^{\delta\tau_2}}{\alpha}.$$

1. If $Z = 0$, then equations $(5.3.2)_1$ to $(5.3.2)_3$ become

$$\begin{cases} S\left(r - d - rkS - \left(rk + \frac{p\beta}{c}\right) I\right) = 0 \\ I\left(\frac{p\beta}{c} e^{-d\tau_1} S - \delta\right) = 0 \\ V = \frac{pI}{c} \end{cases} \tag{5.3.3}$$

Solving $(5.3.3)_2$ we obtain $I = 0$, or $S = \frac{\delta c e^{d\tau_1}}{p\beta}$.

a) If $I = 0$, then from equation $(5.3.3)_3$ gives $V = 0$.Moreover, from $(5.3.3)_1$, we have $S = 0$ leading to the trivial equilibrium point

$$\Theta = (0, 0, 0, 0)$$

or $S = S_0 = \dfrac{r-d}{rk}$ leading to the virus-free equilibrium

$$VFE = (S_0, 0, 0, 0).$$

b) If $S = \frac{\delta c e^{d\tau_1}}{p\beta}$, then by substituting this into equation $(5.3.3)_1$ we obtain

$$r - d - rk(\frac{\delta c e^{d\tau_1}}{p\beta}) - (rk + \frac{p\beta}{c})I = 0.$$

Solving for I leads to

$$I = \frac{c\,(r-d)}{rkc + p\beta} - \frac{rk\delta c^2 e^{d\tau_1}}{p\beta\,(rkc + p\beta)}.$$

Recall that

$$\mathcal{R}_{\tau_1} = \frac{(r-d)\beta p}{rk\delta c e^{d\tau_1}},$$

then

$$I = \frac{rk\delta c^2 e^{d\tau_1}}{p\beta(rkc + p\beta)}\left(\mathcal{R}_{\tau_1} - 1\right).$$

Substituting back into the equations of (5.3.3), we obtain the virus-infected equilibrium (VIE)

$$VIE = \left(\frac{S_0}{\mathcal{R}_{\tau_1}}, \frac{rk\delta c^2 e^{d\tau_1}}{p\beta\,(rkc + p\beta)}\left(\mathcal{R}_{\tau_1} - 1\right), \frac{rk\delta c e^{d\tau_1}}{\beta\,(rkc + p\beta)}\left(\mathcal{R}_{\tau_1} - 1\right), 0\right) \tag{5.3.4}$$

Note that VIE is biologically feasible if and only if $\mathcal{R}_{\tau_1} \geq 1$.

If $Z \neq 0$, then by equation $(5.3.2)_4$ we obtain that

$$I = \frac{b e^{\delta_{\tau_2}}}{\alpha}$$

and consequently, from $(5.3.2)_3$, we have

$$V = \frac{pb e^{\delta_{\tau_2}}}{c\alpha}.$$

Substituting these two expressions back into $(5.3.2)_1$ and $(5.3.2)_2$, we obtain

$$\begin{cases} S\left(r-d-rkS-\left(rk+\frac{p\beta}{c}\right)\frac{be^{\delta\tau_2}}{\alpha}\right)=0 \\ Z=\frac{\delta}{\gamma}\left(\frac{p\beta}{c}e^{-d\tau_1}S-1\right). \end{cases} \tag{5.3.5}$$

$(5.3.5)_1$ implies that $S=0$ or $r-d-rkS-\left(rk+\frac{p\beta}{c}\right)\frac{be^{\delta\tau_2}}{\alpha}=0$. But from $(5.3.5)_2$ we obtain that $S\neq 0$ otherwise $Z=-\frac{\delta}{\gamma}<0$, Hence $r-d-rkS-\left(rk+\frac{p\beta}{c}\right)\frac{be^{\delta\tau_2}}{\alpha}=0$ which leads to

$$S=\frac{r-d}{rk}\left(1-\frac{rkc+p\beta}{c\,(r-d)}\frac{be^{\delta\tau_2}}{\alpha}\right)=S_0\left(1-q\frac{b}{\alpha}e^{\delta\tau_2}\right)$$

where $q:=\frac{b(rkc+p\beta)}{\alpha c(r-d)}$.
Substituting the expressions of $\mathcal{R}_{\tau_1}$ and S into $(5.3.5)_2$ we obtain

$$\begin{aligned} Z &= \frac{\delta}{\gamma}\left(\frac{p\beta}{c}e^{-d\tau_1}S-1\right)=\frac{\delta}{\gamma}\left(\frac{p\beta}{c}e^{-d\tau_1}S_0\left(1-q\frac{b}{\alpha}e^{\delta\tau_2}\right)-1\right) \\ &= \frac{\delta}{\gamma}\left(R_{\tau_1}\left(1-q\frac{b}{\alpha}e^{\delta\tau_2}\right)-1\right) \end{aligned}$$

This gives us the interior equilibrium point

$$\bar{E}=\left(S_0\left(1-q\frac{b}{\alpha}e^{\delta\tau_2}\right),\frac{be^{\delta\tau_2}}{\alpha},\frac{pbe^{\delta\tau_2}}{c\alpha},\frac{\delta}{\alpha}\left(R_{\tau_1}\left(1-q\frac{b}{\alpha}e^{\delta\tau_2}\right)-1\right)\right).$$

For the interior equilibrium point to make biological sense, we must have the following conditions

$$\begin{cases} q\frac{b}{\alpha}e^{\delta\tau_2}<1 \\ \mathcal{R}_{\tau_1}\left(1-q\frac{b}{\alpha}e^{\delta\tau_2}\right)>1 \end{cases}$$

which is equivalent to

$$q\frac{b}{\alpha}e^{\delta\tau_2}<1-\frac{1}{\mathcal{R}_{\tau_1}}.$$

Proposition 5.3.1. *1. If $\mathcal{R}_{\tau_1}<1$ then, system (5.3.2) has two non-negative equilibrium points: the trivial equilibrium point*

$$\Theta=(0,0,0,0),$$

which is not stable, and the virus-free equilibrium point

$$VFE=(S_0,0,0,0)$$

which is locally asymptotically stable.

2. *If $\mathcal{R}_{\tau_1} > 1$ then, in addition to the trivial equilibrium point Θ and the VFE, system (5.3.2) has a virus-infected equilibrium point*

$$VIE = \left(\frac{S_0}{\mathcal{R}_{\tau_1}}, \frac{rk\delta c^2 e^{d\tau_1}}{p\beta\left(rkc + p\beta\right)}\left(\mathcal{R}_{\tau_1} - 1\right), \frac{rkc\delta e^{d\tau_1}}{\beta\left(rkc + p\beta\right)}\left(\mathcal{R}_{\tau_1} - 1\right), 0 \right).$$

Moreover,

   a) *If $q\frac{b}{\alpha}e^{\delta\tau_2} > 1 - \frac{1}{\mathcal{R}_{\tau_1}}$ then (5.3.2) has three equilibrium points: Θ, VFE and VIE.*

   b) *If $q\frac{b}{\alpha}e^{\delta\tau_2} < 1 - \frac{1}{\mathcal{R}_{\tau_1}}$, then, in addition to Θ, VFE and VIE, system (5.3.2) has an interior equilibrium point given by*

$$\bar{E} = \left(S_0\left(1 - q\frac{b}{\alpha}e^{\delta\tau_2}\right), \frac{be^{\delta\tau_2}}{\alpha}, \frac{pbe^{\delta\tau_2}}{c\alpha}, \frac{\delta}{\gamma}\left(\mathcal{R}_{\tau_1}\left(1 - q\frac{b}{\alpha}e^{\delta\tau_2}\right) - 1\right)\right).$$

Proof. The existence of the equilibrium points was discussed in the beginning of this section. The stability of Θ is determined by the roots of the characteristic equation

$$\det\begin{pmatrix} r - d - \lambda & 0 & 0 & 0 \\ 0 & -\delta - \lambda & 0 & 0 \\ 0 & p & -c - \lambda & 0 \\ 0 & 0 & 0 & -b - \lambda \end{pmatrix} = 0,$$

with roots $r - d, -\delta, -c$ and $-b$. Hence Θ is locally asymptotically stable if and only $r < d$.

The stability analysis of VFE, VIE and $\bar{E}$ involve more complicated transcendental equations and is therefore omitted. The simulations presented in the next section suggest some stability results. □

Remark 5.3.2. *The condition $q\frac{b}{\alpha}e^{\delta\tau_2} < 1 - \frac{1}{\mathcal{R}_{\tau_1}}$, that ensures the feasibility of the interior equilibrium point, is equivalent to*

$$\tau_2 < \frac{1}{\delta}\ln\left[\frac{\alpha}{qb}\left(1 - \frac{1}{\mathcal{R}_{\tau_1}}\right)\right]$$

or

$$\frac{\alpha}{b} > \left(\frac{e^{-\delta\tau_2}}{q}\left(1 - \frac{1}{\mathcal{R}_{\tau_1}}\right)\right)^{-1}$$

This shows that for an antiviral response to persist, the immune response must 1) be fast enough ($\tau_2 < \frac{1}{\delta}\ln\left[\frac{\alpha}{qb}\left(1 - \frac{1}{\mathcal{R}_{\tau_1}}\right)\right]$) or strong enough ($\frac{\alpha}{b} > \left(\frac{e^{-\delta\tau_2}}{q}\left(1 - \frac{1}{\mathcal{R}_{\tau_1}}\right)\right)^{-1}$), that is the production rate of immune cells (α) is large enough compared to the death rate of immune cells (b).

Proposition 5.3.3. *The interior equilibrium point $\bar{E}$ is biologically feasible if and only if*

$$\tau_1 < \tau_{1d} := \frac{1}{d} \ln\left(\mathcal{R}_0\left(1 - q\frac{b}{\alpha}e^{\delta\tau_2}\right)\right) \tag{5.3.6}$$

with

$$\tau_{1d} > 0 \text{ if and only if } \tau_2 < \tau_{2d} := \frac{1}{\delta} \ln\left(\frac{1 - \frac{1}{\mathcal{R}_0}}{Q_0}\right). \tag{5.3.7}$$

Proof. The interior equilibrium point $\bar{E}$ is biologically feasible only when $q\frac{b}{\alpha}e^{\delta\tau_2} < 1 - \frac{1}{\mathcal{R}_{\tau_1}}$, which is equivalent to

$$\frac{1}{\mathcal{R}_{\tau_1}} < 1 - q\frac{b}{\alpha}e^{\delta\tau_2}$$

that is

$$\frac{1}{1 - q\frac{b}{\alpha}e^{\delta\tau_2}} < \mathcal{R}_{\tau_1} := \mathcal{R}_0 e^{-d\tau_1}$$

Hence

$$\tau_1 < \frac{1}{d} \ln\left(\mathcal{R}_0\left(1 - q\frac{b}{\alpha}e^{\delta\tau_2}\right)\right) := \tau_{1d}.$$

Note that, $\tau_{1d} < \tau_{1c}$ moreover, $\tau_{1d} > 0$ if and only if $\mathcal{R}_0\left(1 - q\frac{b}{\alpha}e^{\delta\tau_2}\right) > 1$, that is $\tau_2 < \frac{1}{\delta} \ln\left(\frac{1-\frac{1}{\mathcal{R}_0}}{Q_0}\right) := \tau_{2d}$ □

Using the above proposition, we deduce the following theorem that relates the models' delays to the existence of equilibrium points.

Theorem 5.3.4. 1. *If $\tau_1 > \tau_{1c}$ then system (5.3.2) has exactly two equilibrium points: the trivial equilibrium point*

$$\Theta = (0, 0, 0, 0)$$

which is unstable and the virus-free equilibrium and the virus-free equilibrium

$$VFE = (S_0, 0, 0, 0).$$

which is locally asymptotically stable.

2. *If $\tau_1 < \tau_{1c}$ then, in addition to the trivial equilibrium point Θ and the VFE, system (5.3.2) has an virus-infected equilibrium point*

$$VIE = \left(\frac{S_0}{\mathcal{R}_{\tau_1}}, \frac{rk\delta c^2 e^{d\tau_1}}{p\beta\left(rkc + p\beta\right)}\left(\mathcal{R}_{\tau_1} - 1\right), \frac{rkc\delta e^{d\tau_1}}{\beta\left(rkc + p\beta\right)}\left(\mathcal{R}_{\tau_1} - 1\right), 0\right).$$

Moreover,

a) If $\tau_2 > \tau_{2d}$, then (5.3.2) has three equilibrium points: Θ, VFE and VIE.

b) If $\tau_2 < \tau_{2d}$ then $\tau_{1d} > 0$ and we have

i. $\tau_1 > \tau_{1d}$, then (5.3.2) has three equilibrium points: Θ, VFE and VIE.

ii. $\tau_1 < \tau_{1d}$, then, in addition to Θ, VFE and VIE, system (5.3.2) has an interior equilibrium point given by

$$\bar{E} = \left(S_0 \left(1 - q\frac{b}{\alpha} e^{\delta\tau_2} \right), \frac{be^{\delta\tau_2}}{\alpha}, \frac{pbe^{\delta\tau_2}}{c\alpha}, \frac{\delta}{\gamma} \left(\mathcal{R}_{\tau_1} \left(1 - q\frac{b}{\alpha} e^{\delta\tau_2} \right) - 1 \right) \right).$$

Concerning the total tumor size at equilibrium (denoted TTS_{τ_1,τ_2}) we have the following proposition:

Theorem 5.3.5. *1. If $\tau_2 > \tau_{2d}$, then*

a) If $\tau_1 > \tau_{1c}$, then

$$TTS_{\tau_1,\tau_2} = S_{0.}$$

b) If $\tau_1 < \tau_{1c}$, then

$$TTS_{\tau_1,\tau_2} = TTS_{\tau_1} := \frac{S_0}{\mathcal{R}_{\tau_1}} + \frac{rk\delta c^2 e^{d\tau_1}}{p\beta\left(rkc + p\beta\right)} \left(\mathcal{R}_{\tau_1} - 1 \right)$$

2. If $\tau_2 < \tau_{2d}$ then $\tau_{1d} > 0$ and we have

a) $\tau_1 > \tau_{1d}$, then

$$TTS_{\tau_1,\tau_2} = TTS_{\tau_1} := \frac{S_0}{\mathcal{R}_{\tau_1}} + \frac{rk\delta c^2 e^{d\tau_1}}{p\beta\left(rkc + p\beta\right)} \left(\mathcal{R}_{\tau_1} - 1 \right)$$

b) $\tau_1 < \tau_{1d}$, then,

$$TTS_{\tau_1,\tau_2} = TTS_{\tau_2} := S_0 \left(1 - q\frac{b}{\alpha} e^{\delta\tau_2} \right) + \frac{be^{\delta\tau_2}}{\alpha}.$$

The results above are illustrated in the following bifurcation diagrams:

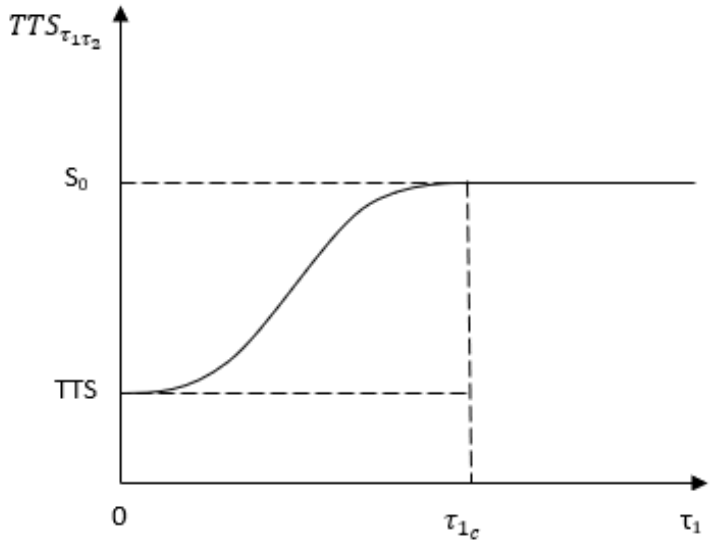


Figure 5.5: Bifurcation diagram of TTS_{τ_1,τ_2} with respect to τ_1 when $\tau_2 > \tau_{2d}$

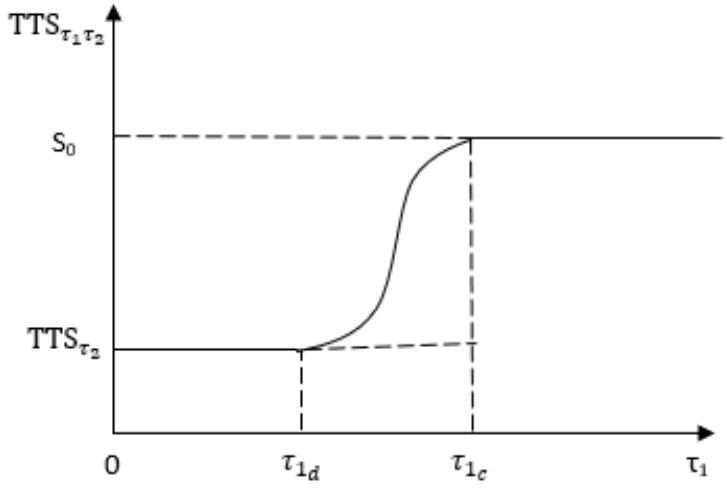
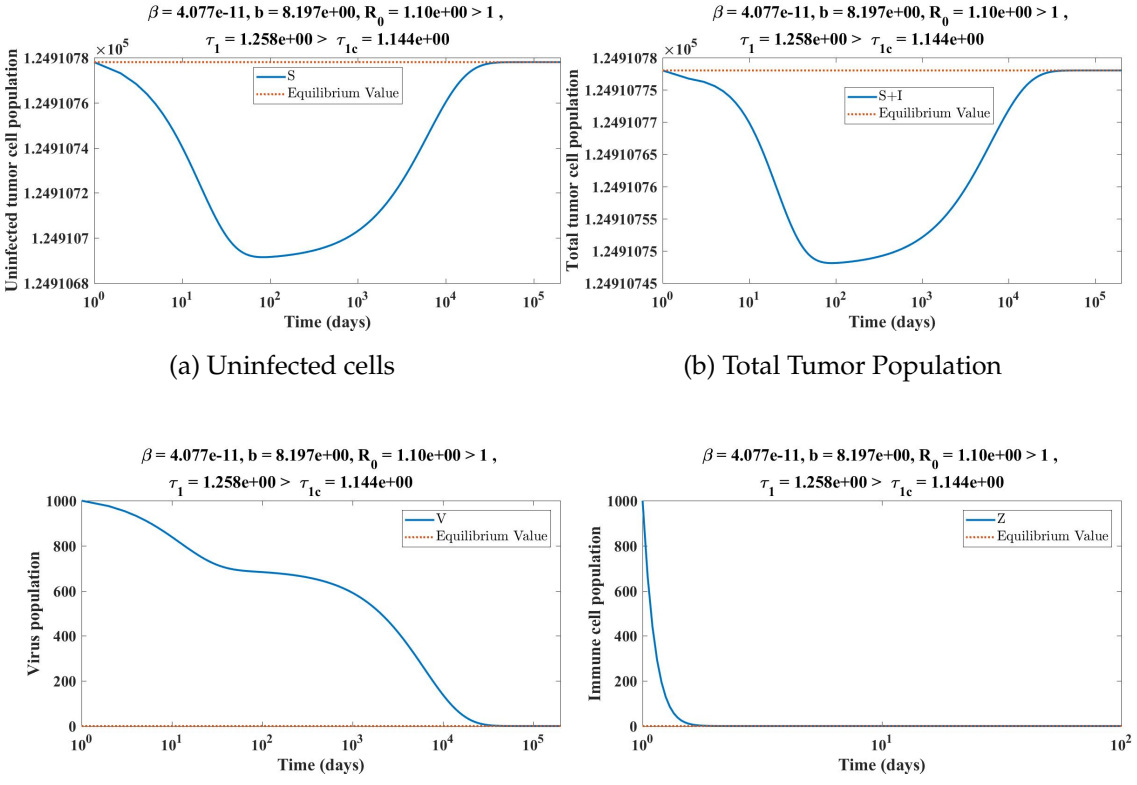


Figure 5.6: Bifurcation diagram of TTS_{τ_1,τ_2} with respect to τ_1 when $\tau_2 < \tau_{2d}$

5.4 Model simulations

We used MATLAB DDE23 solver to perform our simulations and for the sake of these simulations we use parameter values from table 4.1 and choose three values of τ_1 : $1.1\tau_{1c}, 0.9\tau_{1c}, 0.09\tau_{1c}$, we also choose two values of τ_2 : $1.1\tau_{2c}, 0.1\tau_{2c}$ and two values of b : $1.1b_c, 0.9b_c$ where $b_c = \frac{1-\frac{1}{R_0}}{Q_1}$. This will ensure that we cover all the cases discussed in Theorems 5.3.4 and 5.3.5.

We note that due to the long time the model takes to reach equilibrium, we chose our initial conditions close enough to the model equilibrium points to ensure a fast convergence of the model. While this choice is useful in "confirming" our mathematical finding, it has the disadvantage that the model's solutions do not deviate much from the initial condition.



(a) Uninfected cells

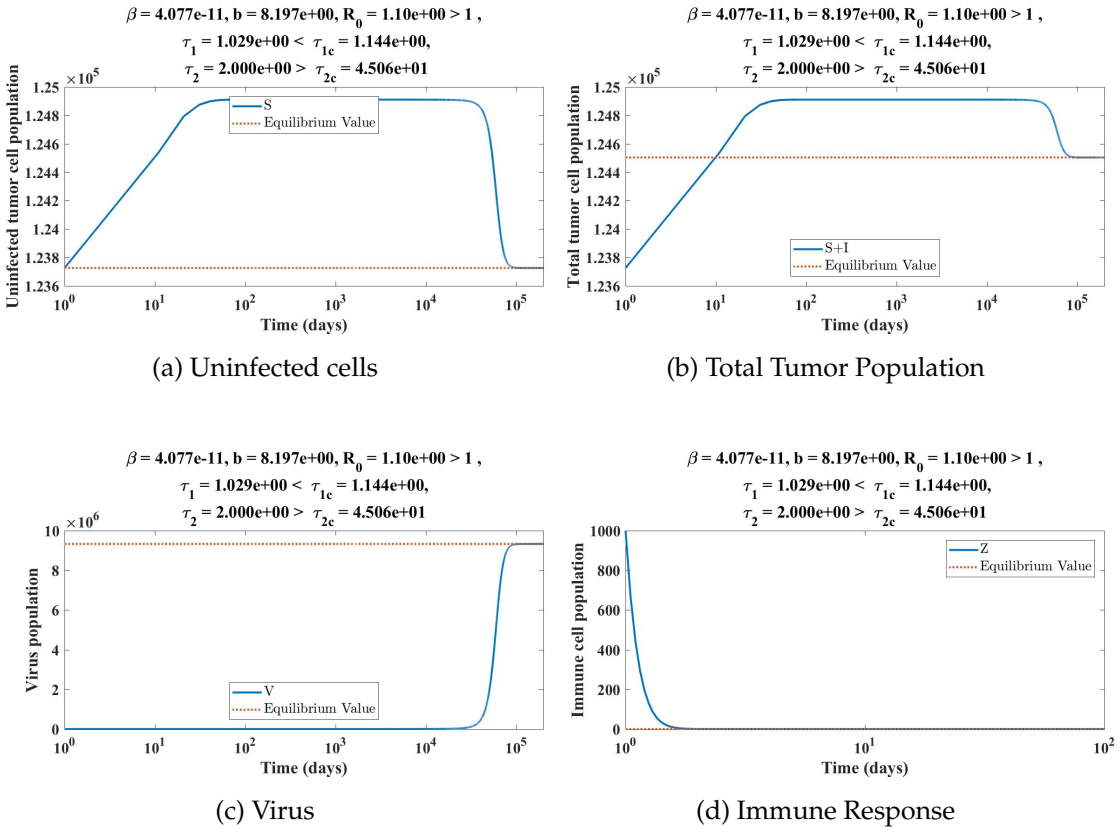
(b) Total Tumor Population

(c) Virus

(d) Immune Response

Figure 5.7: Parameter values used for these figures are $\beta = 4.077 * 10^{-11}$, b = 8.197 with $\mathcal{R}_0 > 1 = 1.10$, $\tau_1 > \tau_{1c}$

Both the uninfected tumor population and that of the total tumor population exhibit a similar behaviour. Although not sharp, we observe a decline at the onset of the treatment sustained for about three months. Thereafter, the tumor cells begin to increase once again to stabilize at the virus-free equilibrium point $(S_0, 0, 0, 0)$ which is locally asymptotically stable $(5.3.4)_1$. We could attribute this to a strong immune response (which is not the case as depicted by sub figure 1d). This only then leads us to conclude that a strong and/or fast oncolytic effect are the contributing factors. We verify the strength since the reproductive number, $\mathcal{R}_0 > 1$; but cannot say the same for the speed as $\tau_1 > \tau_{1c}$ which would in turn imply that $\mathcal{R}_{\tau_1} < 1$. The virus population also decreases over a few years to reach the equilibrium. Also in line with theorem 5.3.4 (1), it is important to note that the tumor size is at its lowest,that is, $TTS_{\tau_1,\tau_2} = S_0$. $(5.3.5)_{1a}$



(a) Uninfected cells

(b) Total Tumor Population

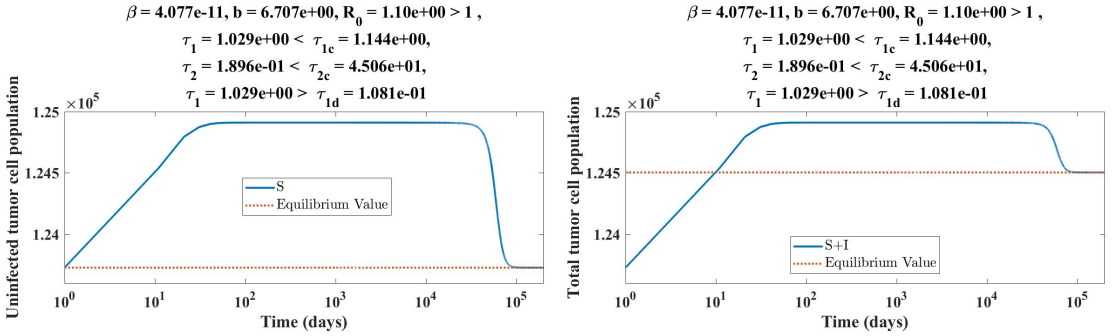
(c) Virus

(d) Immune Response

Figure 5.8: Parameter values used are $\beta = 4.077 * 10^{-11}$, b = 8.197 with $\mathcal{R}_0 > 1 = 1.10$, $\tau_1 < \tau_{1c}$ and $\tau_2 > \tau_{2c}$

We now observe that uninfected tumor cell population (2a) increases within the first

100 days and stays roughly the same size for the next couple of years before eventually shrinking down to the equilibrium. As for the total tumor population, treatment starts before the tumor attains its maximum size and will only show its effect once the tumor reaches a pseudo-steady state. The oncolytic effect of the virus only comes around after so many years when the viruses start replicating but soon reach the equilibrium. The virus-free equilibrium, $VFE = (S_0, 0, 0, 0)$ is locally asymptotically stable $(5.3.4)_{2a}$ and the total tumor size for this case is $TTS_{\tau_1,\tau_2} = TTS_{\tau_1} := \frac{S_0}{\mathcal{R}_{\tau_1}} + \frac{rk\delta c^2 e^{d\tau_1}}{p\beta(rkc+p\beta)}(\mathcal{R}_{\tau_1} - 1)$ as depicted by the Theorem $(5.3.5)_{1b}$.



(a) Uninfected cells

(b) Total Tumor Population

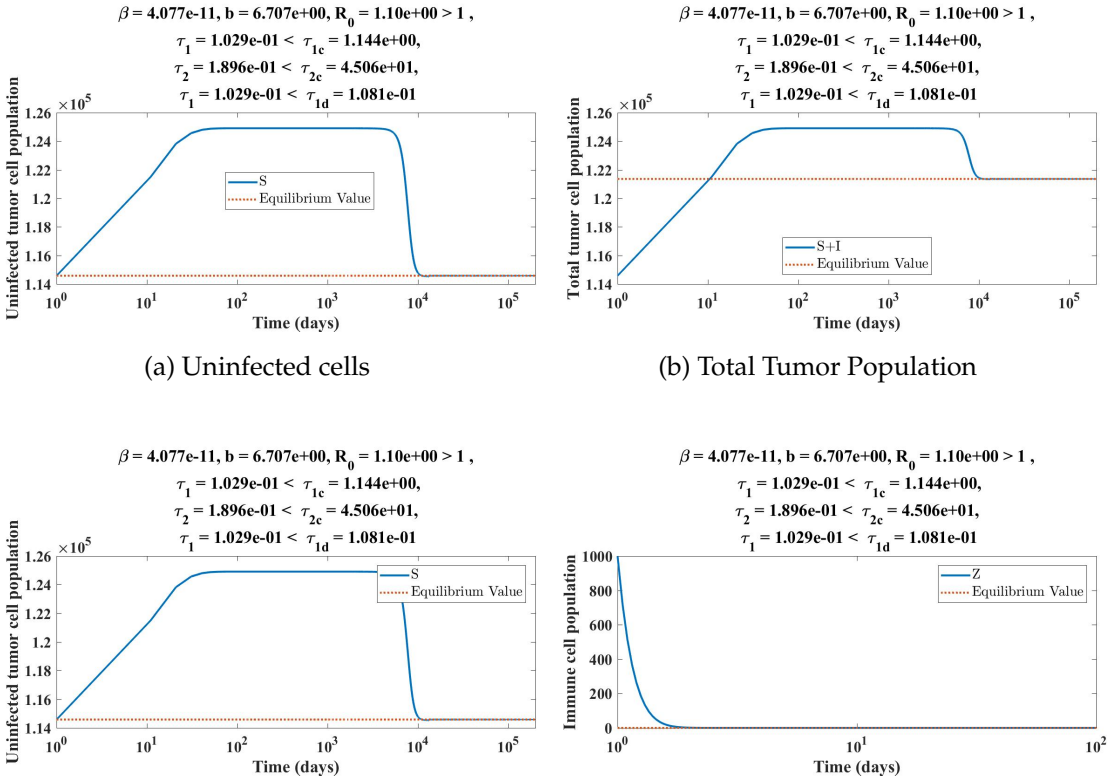
(c) Virus

(d) Immune Response

Figure 5.9: Parameter values used include: $\beta = 4.077 * 10^{-11}$, b = 6.707 with $R_0 > 1 = 1.10$, $\tau_1 < \tau_{1c}$, $\tau_2 < \tau_{2c}$ and $\tau_1 > \tau_{1d}$

In this case, we note that $\tau_{1d} > 0$. The system 5.3.1, has a locally asymptotically stable virus-free equilibrium point $VFE = (S_0, 0, 0, 0)$ $(5.3.4)_{2b}$. The uninfected tumor cell population gradually increases over slightly more than three months and maintains the size for the next couple of years before eventually shrinking down to the equilibrium.

A similar trend is observed from the total tumor cell population graph (3b). Oncolytic virotherapy does not commence until the tumor cannot grow any further and its effects will only be observed at a pseudo-steady state. The immune cell population in 3d from the diagram seems to be intersecting at the equilibrium at what may seem to be a zero value due to the choice of our parameters but in the actual sense, it converges to a non-zero value of z. Total tumor size is $TTS_{\tau_1,\tau_2} = TTS_{\tau_1} := \frac{S_0}{\mathcal{R}_{\tau_1}} + \frac{rk\delta c^2 e^{d\tau_1}}{p\beta(rkc+p\beta)}(\mathcal{R}_{\tau_1} - 1)$.



(a) Uninfected cells

(b) Total Tumor Population

(c) Virus

(d) Immune Response

Figure 5.10: Parameter values used in this figure are $\beta = 4.077 * 10^{-11}$, b $= 6.707$ with $R_0 > 1 = 1.10$, $\tau_1 < \tau_{1c}$, $\tau_2 < \tau_{2c}$ and $\tau_1 < \tau_{1d}$

We have a couple of equilibrium points for the system (5.3.1) at this point with the virus-free equilibrium point $VFE = (S_0, 0, 0, 0)$ being locally asymptotically stable, the virus-infected equilibrium point $VIE = ((\frac{S_0}{\mathcal{R}_{\tau_1}}, \frac{rk\delta c^2 e^{d\tau_1}}{p\beta(rkc+p\beta)}(\mathcal{R}_{\tau_1} - 1), \frac{rkc\delta e^{d\tau_1}}{\beta(rkc+p\beta)}(\mathcal{R}_{\tau_1} - 1), 0))$ and an interior equilibrium point $\bar{E} = (S_0(1 - q\frac{b}{\alpha}e^{\delta\tau_2}), \frac{be^{\delta\tau_2}}{\alpha}, \frac{pbe^{\delta\tau_2}}{c\alpha}, \frac{\delta}{\gamma}(\mathcal{R}_{\tau_1}(1 - q\frac{b}{\alpha}e^{\delta\tau_2}) - 1))$ also stable. The total tumor size is, $TTS_{\tau_1,\tau_2} = S_0\left(1 - q\frac{b}{\alpha}e^{\delta\tau_2}\right) + \frac{be^{\delta\tau_2}}{\alpha}$ which is line with

theorems $(5.3.4)_{bii}$ and $(5.3.5)_{2b}$. The uninfected tumor cell population grows gradually over three months before plateauing for the next several years to suddenly start quickly dying off to the equilibrium. As for the immune response, the effect is minimal as it quickly diminishes to the equilibrium at zero.

Chapter 6

Discussion and Conclusion

6.1 Introduction

We discuss the various findings both mathematically and analytically analysed and detail our overall findings.

6.2 Discussion

For many years since the discovery of cancer, many treatment methods have been adopted such as surgery, radiotherapy, chemotherapy among others. While these treatments did relieve patients either of pain, tumor size reduction or both, they were not entirely successful. One of their main disadvantages was affecting normal cells. Therefore, researchers, doctors and scientists sought a better treatment method to relieve people of this epidemic burden of cancer.

This was the birth of Oncolytic virotherapy. This treatment involves the intravenous introduction of oncolytic viruses into tumors. Unlike the other modes of treatment, the oncolytic viruses only affect the tumor cells and leave normal, healthy cells intact making them a favourable mode of cancer treatment.

These viruses are fairly new anticancer agents, still under study and clinical trials. As earlier mentioned, they were discovered by 'sheer luck' when leukemia and Hodgkins lymphoma patients suffered from influenza and hepatitis respectively. It was realized that contracting these viral diseases had a direct influence on the shrinking of their tumors and improvement of the patients' white blood cell counts.

More recently, studies have been focusing on the direct antitumor properties of the oncolytic viruses. Even though there is mounting evidence that the host immune response may be hinder the efficacy of oncolytic virotherapy as a cancer mitigation method, its effect may be aided in a few ways such as through: inherent immune effectors, adaptive antiviral immune responses which alienate infected cells or adaptive antitumor immune responses.

Apart from the effects of reactions from the immune response, we looked at a simultaneous model of both immune response and intracellular delay. We sought to find a point where we could effectively minimise the turnaround time of viral replication making them speedily replicate while at the same time, trying to reach a point where the immune response is slow enough not to attack the oncolytic viruses to help in achieving optimum tumor cells reduction.

For simplicity, we assumed that the infection rate takes the mass action form rather than other more complicated forms. Mass action is a fitting method of approximation as the total population of tumor cells and oncolytic viruses remains fairly constant. Broadly, it assumes that the contact rate grows intrinsically as the population of virons and cells also grows, meaning, the density of the population is proportional to the total amount of tumor cells and oncolytic viruses. (Crivelli *et al.*, 2012) (Novozhilov *et al.*, 2006)

We ran simulations with the help of the DDE23 MATLAB solver using parameters gathered from literature review to substantiate these findings. Against a number of days, we sought to analyse different populations: the uninfected tumor cell population, the total tumor cell population which encompassed both the uninfected and infected tumor cells, the viral population as well as the immune response.

The different set of graphs we got for each set of parameters confirmed our prior mathematical findings where we could balance out the outcome of the immune system as well as the replication time of the virus with treatment efficacy.

6.3 Conclusion

As seen in the calculations in chapter 4 and the graphs from chapter 5, we deduced that patients can receive oncolytic virotherapy with optimum delay times of both the immune reponse and the replication time of these viruses. In essence, for successful treatment of cancer using this unworn method, one would need to make the immune

response time (τ_2) long enough which essentially translates to the immune system not reacting too fast to the viruses hindering successful tumor reduction or total eradication and concurrently, make the intracellular delay τ_1 short enough. This would mean ensuring that the virus used replicates at a very high speed in the tumor thus also positively eliminating or shrinking the tumor in question.

We can arguably deduce that by taking time delays into consideration we may improve the success rate of the treatment.

6.4 Future Work

This study did not take into account virus-rejecting tumor cells which has been highlighted in some articles as a hindrance from successful virotherapy. We also did not input any data to validate our model. In future, we aim to use a more detailed and complex model taking into account other things such as virus-tumor rejection and data to better understand the role of time delays even further.

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